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PRIMARY MALIGNANT BONE TUMORS*

A Report of Ninety-Three Cases Observed at Pondville Hospital, 1928–1949

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NINETY-THREE cases of primary malignant bone tumor have been observed at the Pondville Hospital in the past twenty-one years. The group under consideration consists of: Ewing's tumor, osteogenic sarcoma, osteogenic sarcoma arising from Paget's disease, chondrosarcoma and periosteal fibrosarcoma. These cases correspond to other reported series in respect to age grouping, sex distribution, site of the primary tumor, presenting symptoms, metastases and longevity. Bone tumors usually manifest themselves early through pain and swelling; methods for definitive diagnosis are easily available; the tumor site is usually accessible for radical therapy. Yet in spite of these seemingly favorable circumstances, the over-all salvage has been poor. Of the 93 patients only 8 have been alive, free of disease, five years after the onset of symptoms. We have analyzed our cases in an attempt to determine factors responsible for such unfavorable end results. No patients have been lost to follow-up.

DISTRIBUTION

The distribution of our cases in respect to classification and sex division is summarized in Table 1. In 88 patients the diagnosis was confirmed histologically by biopsy, operation or autopsy. In the other 5 cases the diagnosis rested on clinical and radiologic findings; these 5 were all osteogenic sarcoma, 3 arising from Paget's disease and all ending fatally. Males outnumbered females in each group, at a ratio of about 2 to 1 for the entire series.

AGE

A primary bone malignancy may occur at any age. Our youngest patient was a five-year-old girl with Ewing's tumor and the oldest was a seventy-six-year-old woman with osteogenic sarcoma. Ewing's tumor did not occur over the age of thirty; the oldest patient in that group was a twenty-seven-year-old man. Osteogenic sarcoma arising from Paget's disease is naturally a disease of the older age group; our youngest was a forty-three-year-old man. The other types were fairly evenly distributed in all age groups after the first decade.

TABLE 1. *Distribution of Tumors According to Sex.*

	MALE	FEMALE	TOTALS
Ewing's tumor	13	4	17
Osteogenic sarcoma	25	13	38
Osteogenic sarcoma on Paget's disease	6	4	10
Chondrosarcoma	15	5	20
Fibrosarcoma	5	3	8
Totals	64	29	93

Almost one half of the total number of cases of the series occurred in the second and third decades (Table 2).

PRIMARY SITES

The location of the neoplasm is important in the consideration of radical curative therapy, tumors of the extremities being the most accessible. Of the 97 primary sites (3 patients had multiple primary sites) about one half (48) were in a bone of the extremities (Table 3). The lower extremity outranked the upper (39 to 9), and the single most commonly involved bone was the femur, usually at its distal portion. Of the flat bones, the pelvic bones were most frequently affected.

TRAUMA

In 88 cases the problem of preceding injury had been considered and noted in the clinical histories. In 64 no injury to the part could be recalled; 24 patients gave a history of injury to the region of the primary site at varying intervals before the onset of symptoms attributed to the bone tumor. The injuries were almost all minor, such as bruises from falls and athletic activities; in only one instance had the trauma been severe enough to cause a

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fracture, in this case of the rib. We agree that the evidence for trauma as a pathogenic factor is not convincing, and that the injury often focuses the attention of the patient on the bone lesion already present; this is manifested in 13 of our patients in whom the symptoms attributable to the neoplasm followed the reported trauma immediately, with no reasonable time interval between supposed "irritative factor" (trauma) and tumor.

Time of Metastasis

Patients with malignant bone disease usually die of metastases rather than from the results of direct extension of the primary tumor. The route of spread is most frequently by the blood stream to the lungs and to other bones. The liver, other viscera and lymph nodes are less often involved. In 48 cases we were able to determine roughly the time interval between the onset of symptoms due to the primary bone tumor and the occurrence of metastases as demonstrated in chest or bone films. Since the metastasis must be present for some time before it can be detected on the roentgenogram, the time intervals as evidenced by the x-ray film must be longer than is actually the case. Even so, 14 of the 48 cases showed metastases within three months of the onset of symptoms. Within nine months metastases were demonstrable in half of the cases. This propensity for rapid distant spread makes early diagnosis imperative, so that curative treatment may be effective while the tumor is still localized.

Table 3. *Primary Sites of Tumor.*

Site	No. of Cases
Pelvic bones	24
Femur	25
Tibia	10
Fibula	3
Foot	1
Humerus	8
Radius	1
Skull	12
Rib	7
Scapula	3
Sternum	1
Spine	2

Delay in Establishing Correct Diagnosis

Data were available in 91 of our cases to allow the determination between time of onset of symptoms and establishment of the correct diagnosis. In over one third of the patients (33) the correct diagnosis was made within three months; in almost two thirds, within six months. The establishment of the diagnosis of a primary bone tumor should not be difficult in most cases. Pain and swelling are the chief symptoms, the pain usually preceding the swelling. Limitation of motion and crippling pain on weight-bearing are later manifestations. In more than one third of the cases symptoms had been present for over three months before a physician was first consulted. The delay, once the patient was under medical care, was of a similar magnitude; in more than one third of the cases over three months elapsed before the correct diagnosis was made. In too many instances the diagnosis of "arthritis," "rheumatism" or "sprain" has been made, and treatment has been instituted on the basis of these incorrect diagnoses. Any patient with persisting bone, joint or muscle pain in the absence of significant immediate trauma is a suspect for a primary bone neoplasm, and further studies are in order. In many instances x-ray examination will suggest the nature of the disease. The nonspecific and often mild early symptoms are apt to delude the physician. The initial medical diagnosis was available in 67 of our cases; bone tumor had been considered in only slightly over one half (36). Traumatic and inflammatory processes were suspected in the rest of the patients. These latter diagnoses included sprain, osteomyelitis, arthritis, rheumatism, sciatica, neuritis and bursitis. Prior to the establishment of the correct diagnosis the forms of treatment varied to a considerable degree and might even be considered harmful in the presence of bone disease. Such measures included local heat, liniments, massage, osteopathic manipulation, incision and drainage, curettage, analgesics and antibiotics.

We do not wish to convey the impression that poor results in the treatment of osseous neoplasms are due primarily to the delay of a few months in diagnosis. Other variables in both the host and the

Table 2. *Age of Patient at Onset of Symptoms.*

Age Group	Ewing's Tumor	Osteogenic Sarcoma	Osteogenic Sarcoma on Paget's Disease	Chondrosarcoma	Fibrosarcoma	Totals
yr.						
0–10	2	—	—	—	—	2
11–20	9	13	—	3	1	26
21–30	6	9	—	2	1	18
31–40	—	3	—	4	—	7
41–50	—	4	1	4	3	12
51–60	—	4	5	2	2	16
61–70	—	4	3	2	1	10
71–80	—	1	1	—	—	2

tumor are undoubtedly of major importance. However, we believe that in bone tumors, as with any malignancy, the earlier the discovery and treatment the better will be the results. Tumors of the same histologic grouping have different rates of growth and spread. The rapidly growing and spreading tumors are likely to produce more severe symptoms and lead to less procrastination on the part of both patient and doctor. Early diagnosis and prompt radical treatment are good policy for any malignancy.

Results

In our 93 cases 30 must be classified as "secondarily treated," that is, the patients had received

Table 4. *Results of Primarily-Treated Cases.*

Mode of Therapy at Pondville	No. of Cases	Alive at 5 Years Free of Disease	Alive at 5 Years with Disease
Curative surgery	24	7	2
Curative x-ray treatment	10	1	1
Curative surgery and x-ray treatment	1	0	0
Palliative surgery	4	0	1
Palliative x-ray treatment	14	0	0
No treatment to primary lesion	10	0	0
Totals	63	8	4

treatment elsewhere before coming to Pondville. Biopsy was not regarded as treatment. None of the secondarily treated patients was alive and free of disease five years after the onset of symptoms, although 1 patient was alive with disease at six and a half years, with a chondrosarcoma of the ilium, treated elsewhere by partial excision of the tumor mass. In this same group no further treatment could be offered to the primary site in 20 cases, palliation being the only remaining measure. Only 3 patients were considered eligible for a curative type of therapy, — surgical in 2 and radiologic in the other, — and with no success. Seven patients were given only palliative measures, such as amputation to relieve pain at the primary site even though metastases were already evident and x-ray therapy in small doses to diminish pain in an inaccessible or widespread tumor.

Sixty-three patients were admitted to Pondville for their primary therapy (Table 4). Ten of these cases had already progressed too widely to warrant any treatment to the primary lesion; none of the patients lived for five years. In 18 only palliative therapy could be employed; as expected, none of this group was alive and free of disease at five years after onset of symptoms, although a patient with chondrosarcoma of the sternum lived for seventy-nine months, having been treated with partial excision. The remaining 35 patients received primary treatment at our hospital; such treatment was of a curative nature — radical surgery or deep x-ray therapy. Of the 24 treated surgically, 9 were alive at five years after the onset of symptoms, 2 with disease and the other 7 free of disease. Of the 10 given radiotherapy, only 2 were alive at five years, one with disease and one without disease. One patient with osteogenic sarcoma of the mandible was treated by a combination of surgery and radiotherapy, with a survival of only eleven months after onset of symptoms.

A further breakdown of the primarily treated cases given radical surgery is of interest. As seen in Table 5, none of the 3 patients with Ewing's tumor lived five years. Twelve patients with osteogenic sarcoma were so treated. Three were lost by postoperative death; 1 died at three years of renal disease with no evidence of cancer. Of the remaining 8 patients 5 were alive at five years, 4 free of disease. Seven patients with chondrosarcoma were treated by radical surgery; 2 are still alive and well, one at forty-four months after the onset of symptoms and the other at fifty-seven months; of the remaining 5, 1 died after eighteen years of pulmonary metastases and 2 are alive at five years, free of disease. Of the 2 patients with fibrosarcomas subjected to curative surgery, one died of metastases at twenty-two months and the other is alive and well at nineteen and a half years. Thus, of eighteen cases who survived the operation and who could be followed for at least five years, 7 were free of disease.

Table 5. *Primary Tumors Treated with Curative Surgery.*

No. of Cases	Ewing's Tumor	Osteogenic Sarcoma	Osteogenic Sarcoma on Paget's Disease	Chondrosarcoma	Fibrosarcoma	Totals
Total no. of cases	3	12	0	7	2	24
Determinate number*	3	8	0	5	2	18
Alive at 5 years, free of disease	0	4	0	2	1	7
Alive at 5 years with disease	0	1	0	1	0	2

*This group excludes operative deaths, intercurrent deaths of other causes and recent cases.

Ten primary cases were subjected to curative radiotherapy: 4 Ewing tumors, 3 chondrosarcomas and 1 each of the other three types. All tumors, except in 4 cases, received at least 5000 r (air). These 4 cases receiving less than 5000 r (air), although given what was considered curative therapy at the time, would be considered undertreated by present standards. Of the 10 patients only 1 was

free of disease at five years, — a patient with Ewing's tumor still alive six and three-quarters years after onset of symptoms. One of the patients with chondrosarcoma is still alive at thirteen and one-half years, though with evidence of disease. The other 8 all died of their disease within five years.

Summary

We consider the following factors of significance in the low salvage rate in cases of primary malignant bone tumors:

In many cases there was an avoidable delay between onset of symptoms and establishment of the correct diagnosis.

Misguided treatment prior to the correct diagnosis has, in some cases at least, very likely prejudiced a favorable outcome.

The relatively large number of patients admitted with invasion beyond the local site or widespread metastases (48 of the 93 patients) obviously diminished the chances for cure.

The large number of cases treated primarily elsewhere has lowered the cure rate in this group.

A sizable proportion of neoplasms in sites inaccessible to adequate surgery has limited attempts at curative surgery. With the possible exception of Ewing's tumor, radical surgery, rather than radiotherapy, appears to be the treatment of choice for the types of tumor evaluated here. Thus, of a total number of 39 neoplasms located in a bone of the lower extremity, curative therapy could be given to about one half (19), and of 9 occurring in the upper extremity such therapy could be applied to 4. On the other hand, of 24 neoplasms occurring in bones of the pelvis, only 5 could be attacked in a curative manner.

For patients with malignant bone tumors so situated that radical surgery of a curative nature can be carried out and in whom there are no evidences of metastases, the outlook is brighter than is generally thought. Of 18 such cases in our group, 7 were alive and free of disease five years after onset of symptoms. Ten patients received primary treatment with substantial dosages of x-ray; one (Ewing's tumor) was cured.

METABOLIC EFFECTS OF THE RICE DIET IN THE TREATMENT OF HYPERTENSION*

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DIETARY measures in the treatment of hypertension have been advocated periodically during the past fifty years and have been extensively reviewed recently.[1] The metabolic effects of the rice diet have been reported previously in abstract form.[2] Although the most recent empirical program, as outlined by Kempner,[3] is of limited value in the treatment of most patients with hypertensive vascular disease because of its rigid restrictions on diet, rather striking improvements in the level of blood pressure and general condition have been observed in some patients. The physiologic changes responsible for such improvement as may occur in these patients are, however, not well identified. Undesirable effects have also been observed.[3-9] Our metabolic studies are reported herewith in the hope that in conjunction with the studies of others they may contribute to the elucidation of both desirable and untoward effects of such dietary therapy.

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Method of Study

Seven patients have been observed on the metabolic ward of this hospital, each one studied periodically for three to six weeks at a time. Observations were made during control periods on a prescribed normal diet and during periods on a diet of rice and fruit (with added vitamins) as advocated by Kempner. Blood-pressure and pulse readings were made 5 times daily, and an average reading was taken for each day. Balance studies of the electrolytes and nitrogen were done. Plasma volume was determined according to the Evans-blue dye technic of Gibson and Evelyn,[10] and the blood volume was calculated from the plasma volume and the hematocrit value. The "thiocyanate space" was determined by the sodium-thiocyanate method as described by Stewart and Rourke.[11] Renal clearances were determined by the mannitol and para-amino-hippurate methods of Smith.[12] Each clearance was repeated 4 times and the average standardized to 1.73 square meters of body surface. The basal metabolic rate was determined by the standard Benedict–Roth technic before and after institution of the dietary program. Protein-bound-iodine studies were done on 3 patients.

Chemical determinations were performed by the following methods: total nitrogen, Kjeldahl; nonprotein nitrogen, Folin[13]; sodium, Butler and Tut-

hill[14]; chloride, Wilson and Ball[15]; potassium, Fiske and Litarczek[16]; calcium, Fiske and Logan[17]; magnesium, Briggs[18]; inorganic phosphorus, Fiske and Subbarow[19]; cholesterol, Bloor[20]; proteins, the macro method of Peters and Van Slyke[21]; urea nitrogen, Van Slyke[22]; protein-bound iodine, Riggs[23]; and 17-ketosteroids, Fraser and others.[24]

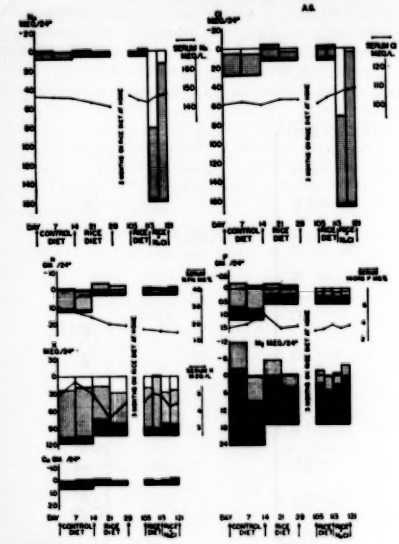

FIGURE 1. *Electrolyte Balance and Average Blood Pressure. Intake is represented by the length of the column below the zero line. The black area represents stool; the cross-hatched area, urine. A positive balance is indicated by a clear area between the top of the cross-hatched area and the zero line; a negative balance is demonstrated by the height of the column above the zero line. The serum values are indicated by the solid line with the accompanying scale on the right.*

RESULTS

Weight

All patients lost weight on the rice diet. The range of weight loss was from 1.5 to 6 kg., with an average of 3 kg. The patient who lost 1.5 kg. in weight (A. G.) regained this weight when given a supplement of 9 gm. of salt per day. The greatest weight loss, — 6 kg. (M. A.), — resulted in a patient who had fluid retention during her control period, as evidenced by mild dependent edema.

Nitrogen

Careful nitrogen-balance studies were carried out on 3 patients, and a significant negative balance was observed during the first week in all patients, ranging from 4 to 5.5 gm. per twenty-four hours (Fig. 1 and 2). Patient A. G. (Fig. 1) had a progressive decrease in the negative nitrogen balance, so that after three months it finally averaged 0.5 gm. of nitrogen per day. A significant decrease in the serum nonprotein nitrogen was also noted.

Considerable argument has developed concerning whether patients on the rice-and-fruit diet undergo starvation. This, of course, depends on the definition of the term. From the standpoint of caloric intake it could hardly be stated that these patients suffered from starvation. If by the use of the word "starvation" a certain deficiency of protein is denoted, one might regard these patients as suffering from starvation. "Deprivation" might be a better term to use for this phenomenon,

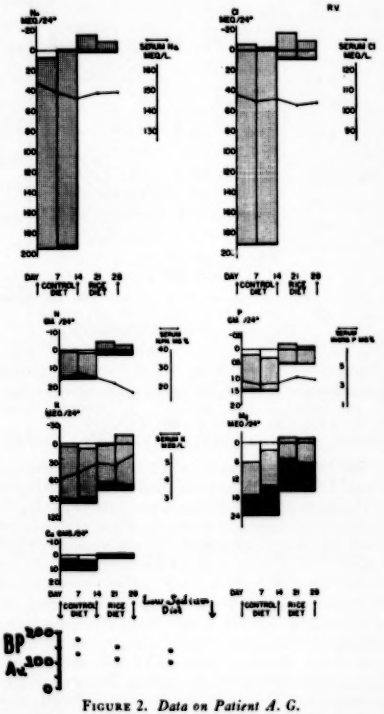

FIGURE 2. *Data on Patient A. G.*

since there was no sign that the patients suffered appreciably from this low-protein intake.

It is significant that after a period of several weeks the negative nitrogen balance diminishes and equilibrium is approximated or equaled after several months.[25] It has been known for some time that a sizable store of nitrogen is available in the body that can be used without serious handicap to the patient as long as the caloric intake remains

		P.V.	B.V.	T.S-P.V.
M.A.	CONTROL	3.6 ↓	6.0 ↓	13.6 ↓
	RICE	2.3	4.4	10.6
J.K.	CONTROL	3.2 ↓	4.9 ↓	12.0 ↓
	RICE	2.3	4.4	9.3
W.K.	CONTROL	2.7	5.4	7.4
	RICE	2.6	5.2	7.9
A.G.	CONTROL	3.2 ↓	5.9 ↓	14.0
	RICE	2.8	4.7	14.8
	AFTER NaCl 9GM. / DAY	2.7	4.9	12.9 ↓
R.V.	CONTROL	3.9	7.2	14.5
	RICE	3.9	7.1	15.8
P.W.	CONTROL	3.0-3.9	4.8-6.5	15.8-13.8
	RICE	3.4	5.5	14.7

P.V.= PLASMA VOLUME
B.V.= BLOOD VOLUME
T.S.= THIOCYANATE SPACE

FIGURE 3. *Plasma Volume, Blood Volume and Thiocyanate Space in 7 Patients.*
The arrow indicates significant change.

adequate.[26] The fall in serum protein already noted in one case (A. G.) was most likely related to the protein deprivation.

Plasma, Blood and "Thiocyanate-Space" Volume

The plasma volume was determined on the house diet and at least two weeks after institution of the rice-and fruit diet in 6 patients (Fig. 3). No significant change was observed in 3 of the patients; these included 1 patient (R. V.) who seemed to have a significant change in blood pressure, as mentioned under "Basal Metabolic Rate." Significant decrease of plasma volume was observed in 3 patients, one of whom (A. G.) had a significant change in blood pressure. The blood-volume change was similar to that of the plasma volume. The thiocyanate space (other than plasma volume — Fig. 3) decreased in 2 patients and was not significantly altered in 4. A slight decrease was noted in 1 patient after the addition of 9 gm. of sodium chloride per day.

Absolute plasma volume is recognized as being difficult to determine accurately by the method used, but the method should be of value in detecting serial changes in the same patient. In 3 patients there was a significant decrease in plasma volume; in the other 3 there was no change. No correlation was found between the change of plasma volume and change in blood pressure. In a considerably larger series of patients, Murphy[27] found an average decrease in plasma volume and interstitial-fluid volume of about 10 and 12 per cent respectively. He, too, noted the lack of correlation between change in plasma volume and change in blood pressure.

Serum Protein

The serum-protein determinations were carried out in 5 patients who had been on the rice diet from one to four months. A fall in protein occurred in 1 patient (A. G.), from 7 gm. to 5.6 gm. per 100 cc., after three months of the rice-and-fruit diet. The fall in serum globulin was slightly greater, proportionately, than the fall in serum albumin. No significant change was noted in the other 4 patients.

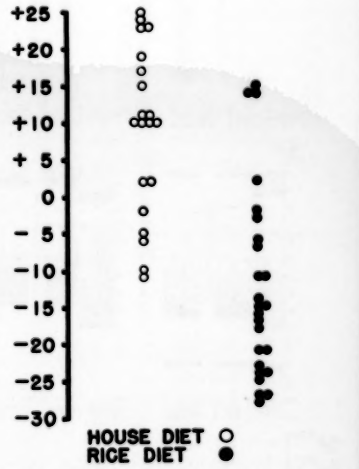

FIGURE 4. *Basal Metabolic Rates of 7 Patients on House Diet and on Rice Diet (Multiple Determinations on Each Patient).*

Basal Metabolic Rate

The basal metabolic rate was found to decrease in all cases after the rice-and-fruit diet was instituted. The degree of change is noted in Fig. 4. The change was found to occur rather soon after institution of the diet; little further drop was noted after two weeks on the diet. Significant change was noted in the 2 patients in whom changes in blood pressure occurred (R. V. and A. G.).

The fall in basal metabolic rate was thought to be a significant observation in these patients. An average decrease of 11 per cent was noted by Watkin and his co-workers[28] in some 43 patients. It is to be noted that the fall in basal metabolic rate occurred simultaneously with the decrease in the negative nitrogen balance. One could not regard a fall in the basal metabolic rate as the result

of a decrease in the specific dynamic action of protein, as the basal metabolic rates were determined under basal conditions some twelve to fifteen hours after absorption. The insensible weight loss was not found to change in 2 patients, although the basal metabolic rate did decrease significantly.

Cholesterol

A general downward trend of the serum cholesterol was noted after instituting the rice diet in 6 of the 7 patients. The average serum cholesterol during the control period was 255 mg. per 100 cc.; on the rice diet it was 184 mg. per 100 cc. This decrease is somewhat comparable to that noted by Kempner[7] but greater than observed by Watkin and others.[28] The fall in serum cholesterol seemed to be more gradual than the fall in the basal metabolic rate.

Protein-Bound Iodine

Protein-bound-iodine studies were made in 3 patients (Fig. 5). The number of determinations is inadequate, but in the few determinations made there was no significant change in the level of the protein-bound iodine.

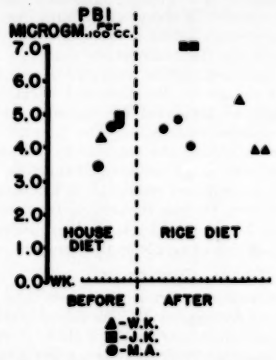

FIGURE 5. *Serum Protein-Bound Iodine Values in 3 Patients Before and After Institution of the Rice Diet.*

In J. K. the apparent increase in protein-bound iodine was associated with a rise in blood pressure and heightened nervous tension attributed to disturbing factors on the ward.

Too few observations on the protein-bound iodine are available for correlation, but it is interesting to note that in those determinations that were made no significant decrease was noted, although the basal metabolic rate did fall. If one wishes to accept the protein-bound iodine as evidence of thyroid function, one could claim that thyroid function has remained unchanged. A low-protein diet is known to alter the function of the adrenal glands,[29] and adrenal function does affect the basal metabolic rate.

Electrolytes

Careful electrolyte-balance studies were done in 3 patients; the results in 2 of these patients are shown in Figures 1 and 2 (A. G. and R. V.). The results of these various balance studies were not dramatic. A negative sodium and chloride balance was noted in 2 of the patients after institution of the diet but was not noted in the third patient (A. G.), who had been maintained on a low-sodium diet before the institution of the rice diet. A positive potassium balance was noted most of the time in one patient (A. G. — Fig. 1) during the control and rice-diet periods. No significant change was observed in the phosphorus, calcium and magnesium balances during either control or rice-diet periods. The electrolyte-balance studies demonstrated no important failure to conserve the various electrolytes in the 3 patients studied.

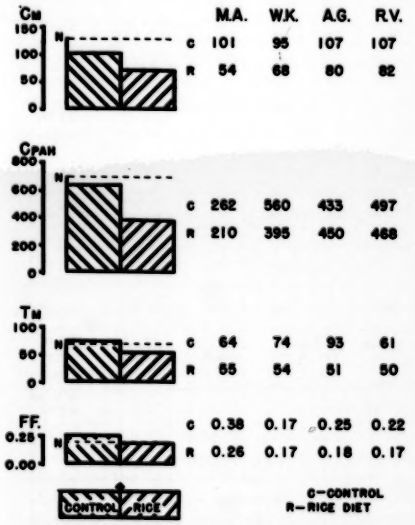

FIGURE 6. *Renal-Clearance Studies on 4 Patients.*

The average change studied is indicated on the left. C_M = clearance of mannitol; C_{PAH} = clearance of para-amino hippurate; T_M = tubular mass; and FF. = filtration fraction.

Changes in the serum levels are noted in Figures 1 and 2. However, no very consistent or apparently significant change in serum values was noted, although the serum sodium decreased slightly.

Renal-Clearance Studies

A decrease in the glomerular filtration rate and effective renal-plasma flow, as measured by the clearance of mannitol and para-amino hippurate respectively, was noted in the 4 patients studied

(Fig. 6). The tubular excretory mass, as measured with hippurate, was found to fall likewise. The filtration fraction, which was slightly above normal, decreased slightly after the diet was instituted.

The change in the renal hemodynamics indicates a general decrease in glomerular filtration, effective renal plasma flow and total tubular excretory mass. The cause of this is not apparent, although it has been demonstrated that both urea clearance and measurable blood flow through the kidney are affected by the amount of protein in the diet.[30-33] The changes observed in this study, therefore, may result from a simple reduction of the protein in the diet and in themselves may not be adverse, as suggested by some workers.[21] There was no correlation between the effects on the renal hemodynamics and those on the blood pressure.

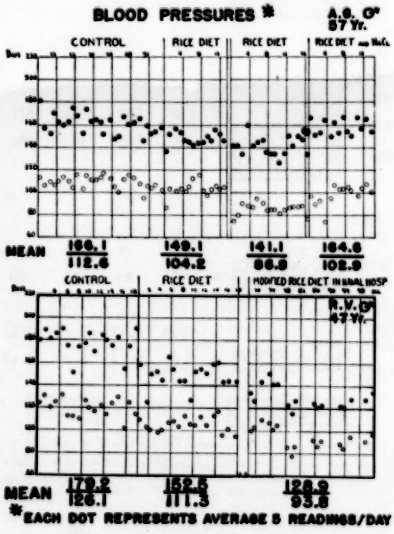

FIGURE 7. *A More Detailed Illustration of the Blood-Pressure Readings on 2 Patients.*

A. G.'s average hospital blood pressure after three years on a low-sodium diet was 175/117.

Urinary Steroids

Only a limited study of the steroid excretion was made before and after institution of the rice diet. A decrease from 13.2 mg. per twenty-four hours to 6.2 mg. per twenty-four hours in the excretion of 17-ketosteroids was noted in 1 man. No change was observed in a woman whose excretions were 5.4 mg. before and 4.8 mg. per twenty-four hours after the rice diet was begun. The patient maintained on the rice diet for the longest period of time (A. G.) was found to have an excretion of 0.12 mg. per twenty-four hours of 11-oxysteroid after ten weeks on the diet.

Blood Pressure

Changes were difficult to evaluate, but the blood pressure was thought to be significantly lowered in 2 patients (A. G. and R. V. — Fig. 7). A rise in blood pressure following the addition of sodium chloride observed in 1 case (A. G.) has been noted by others[25, 35, 36]; no significant change in blood pressure was observed in the other 5 patients, although the trend was downward.

SUMMARY

Seven patients have been observed before and after the institution of the rice-and-fruit diet as advocated by Kempner. Certain metabolic effects have been noted, including a negative nitrogen balance that diminishes progressively and almost reaches balance after two to three months. Slight weight loss was noted in all patients.

A significant fall in basal metabolic rate, with some delayed fall in serum cholesterol, was noted. The protein-bound iodine in the serum was not seen to change in the few observations made.

Renal-clearance studies indicated a general diminution of glomerular filtration and effective renal plasma flow as measured by mannitol and para-amino-hippurate clearances. The plasma volume was found to remain the same or to decrease. No correlation was noted between changes in plasma volume and significant reduction in blood pressure. The blood pressure was thought to be significantly lowered in 2 patients. In 1 of these, it increased after the addition of supplementary sodium chloride.

CONCLUSIONS

The rice-and-fruit diet is of limited value in the treatment of hypertension. The rise in blood pressure with supplementary sodium chloride indicates that the low-sodium content is an important feature of the diet. A decrease in basal metabolic rate has been observed soon after institution of the diet; the cause of this is not clear. The observed decrease in renal clearances during the diet period may reflect only the low-protein content of the diet and is not necessarily an adverse effect. The negative nitrogen balance observed early after institution of the diet diminishes remarkably after several (three to six) months. These data do not clarify the mechanism of the decrease in blood pressure that occurred in 2 of the patients studied.

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ACTH AND CORTISONE IN DISEASES OF THE SKIN*

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BOSTON

MORE than 70 patients with cutaneous diseases have been treated at Massachusetts General Hospital, Peter Bent Brigham Hospital, Robert Breck Brigham Hospital and Children's Hospital with ACTH or cortisone. Although it would be premature to draw definite conclusions, a preliminary evaluation of the results obtained will be attempted.

The fact that ACTH and cortisone are capable of suppressing allergic hypersensitivity reactions as well as inflammatory reactions not solely due to allergy explains the beneficial effect exerted by these drugs on many cutaneous diseases.

In discussing the effects of ACTH and cortisone on cutaneous diseases one can divide these diseases into four groups:

Serious, frequently fatal dermatoses in which ACTH and cortisone represent the best treatment available and in which their use is definitely indicated. To this group belong acute systemic lupus erythematosus, dermatomyositis, pemphigus and chronic idiopathic generalized exfoliative dermatitis. The sooner treatment is started, the better the results obtained.

Acute, self-limited inflammatory dermatoses in which ACTH and cortisone are effective and a short course is indicated if the symptoms are severe enough to warrant such treatment. To this group belong drug eruptions, erythema multiforme, anaphylactoid purpura and contact dermatitis.

Chronic, usually not serious dermatoses in which ACTH or cortisone is indicated only in exceptional cases. To this group belong psoriasis, chronic eczema such as atopic eczema, chronic discoid lupus erythematosus, dermatitis herpetiformis and sarcoidosis. Although ACTH and cortisone produce considerable improvement, these diseases recur quickly on termination of therapy, thus requiring prolonged treatment, with its possible complications.

Chronic, serious dermatoses in which ACTH or cortisone is of little value, as the degree of improvement is usually slight and followed by relapse within a short time. This group includes scleroderma and mycosis fungoides.

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Mode of Administration

It is immaterial whether ACTH or cortisone is administered in the cutaneous diseases just mentioned, because in all these conditions the adrenal glands are capable of responding adequately. For economic reasons the intravenous administration of ACTH is being used with increasing frequency. In general, ACTH given intramuscularly is about 2½ times as effective, milligram for milligram, as cortisone given either intramuscularly or orally, and intravenous administration of ACTH is 5 to 10 times as effective as its intramuscular administration. Most dosages in this presentation are expressed in terms of intramuscularly administered ACTH. The amount should be multiplied by 2½ for oral or intramuscular doses of cortisone and divided by 7 for the corresponding intravenous dose of ACTH.

ACTH, intramuscularly, and cortisone, orally, are given in 4 equally divided doses every six hours. Cortisone, intramuscularly, is given every twelve hours. ACTH is given intravenously, dissolved in 500 ml. of a 5 per cent solution of dextrose, by constant drip over a period of eight hours every day when 20 mg. are given and over a period of twelve hours every day when 30 or 40 mg. are given.[1]

One hundred mg. of ACTH given intramuscularly may be regarded as the average daily dose at the beginning of treatment, but in severe systemic diseases the optimal daily dose is 200 or 300 mg. a day. Children require larger doses than would be expected on a basis of their body weight. Small children should receive about half the adult dose and larger children nearly the adult dose.

In selecting the dosage one must rely above all on the clinical response. ACTH and cortisone act rapidly, and if in a few days clinical improvement has not occurred in the diseases enumerated above it is advisable to increase the dosage. Eosinophil counts[2] need not be performed frequently, but it is advisable to check the number of eosinophils before treatment is started, after the first administration, after one day of treatment and occasionally during the course of treatment. Counts are best made at the time of the maximum effect of the drug, that is, three to four hours after an oral or intramuscular dose or one hour after termination of an intravenous infusion. In some diseases clinical improvement occurs while a fairly large number of eosinophils are still present in the circulating blood, but in most diseases, — particularly in pemphigus, — adequate clinical improvement does not seem to occur until the number of eosinophils (at the time of the maximum effect of the drug) has been reduced to below 50 per cu. mm.

The dangers inherent in the administration of ACTH and cortisone and the precautions necessary to prevent serious complications have been presented in several recent communications[3-8] and for this reason will not be discussed in detail. The most common side-reactions against which one must be on guard are: retention of fluid leading to cardiac decompensation (best averted by restriction of the sodium chloride and fluid intake); hypokalemic alkalosis (prevented by prophylactic administration of potassium chloride, 3 to 6 gm. per day by mouth); reactivation of an old pulmonary tuberculosis or of a peptic ulcer; psychoses; and severe infections. In order to prevent severe, overwhelming infection in very ill or debilitated patients during periods of treatment with ACTH or cortisone, it is advisable to administer concomitantly an antibiotic drug, preferably Chloromycetin, aureomycin or terramycin.

Results of Treatment

Serious, Frequently Fatal Dermatoses in Which ACTH or Cortisone Is Indicated

Acute systemic lupus erythematosus. In acute systemic lupus erythematosus the immediate results are striking. If adequate doses are given, considerable improvement can be observed within two or three days and occasionally in one day. Usually 100 mg. of ACTH given intramuscularly a day is adequate, but severe cases may require daily doses of 200 or even 300 mg., at least at the beginning. Treatment should be continued until the disease is fully in remission. Relapses are the rule and must be controlled either by continued administration of small "maintenance doses" or by repeated courses of large doses. Unfortunately, renal damage, commonly present in patients with acute systemic lupus erythematosus, is not ameliorated by ACTH or cortisone. If treatment is started early before renal symptoms have developed, it appears possible to prevent their development; once severe renal damage has occurred, death from renal failure is inevitable. Even in the absence of renal damage the prognosis must be guarded, as side-reactions from ACTH or cortisone are more prone to develop in acute systemic lupus erythematosus than in most other diseases. This often prevents administration of adequate doses, and the disease thus continues only partially controlled.

Fifteen patients with acute systemic lupus erythematosus have been treated with ACTH or cortisone.[5, 9] Seven have died; 7 are in partial remission and still under treatment; and 1 patient who was treated early and with large doses for many weeks has been in full remission without treatment for over a year. Four of the 7 deaths were due to renal failure.

Dermatomyositis. In dermatomyositis, as in acute systemic lupus erythematosus, adequate doses bring about rapid improvement of the symptoms. One hundred mg., and in severe cases 200 mg., of ACTH given intramuscularly per day is indicated. After a remission has been induced, testosterone

propionate, 50 mg. given intramuscularly, at first every day and later every other day, is of considerable value in maintaining the remission and in restoring muscular tissue by virtue of its faculty of inducing a markedly positive nitrogen balance. Early treatment is important, as after the disease has produced considerable destruction of muscular tissue ultimate improvement of muscular function will be small.

Eight children and 3 adults have been treated.[5, 10] Three children and 1 adult have died of the disease, possibly because of late initiation of treatment or inadequate dosage. Four children and 1 adult are in partial remission and are still receiving testosterone. One child and 1 adult have been in complete remission without treatment for almost a year. One of the children had to receive a second course of ACTH because of reactivation of the disease during administration of testosterone.

Pemphigus. All forms of pemphigus, — pemphigus vulgaris, foliaceus and vegetans, — respond well to ACTH or cortisone. The dosage in severe cases must be high, — as high as 300 mg. of ACTH given intramuscularly per day during the first week or two. If adequate doses are given, new lesions cease to form, in pemphigus vulgaris and vegetans, usually within four to seven days; in pemphigus foliaceus the response is likely to be somewhat slower. After the disease has been brought fully under control by adequate dosage, remissions are often prolonged. The long duration of remissions in some patients has been impressive. Treatment by small maintenance doses, for instance 100 mg. of cortisone given orally, has been found inadequate to suppress the disease. The practice followed at present at the Massachusetts General Hospital is to give a three- to five-week course of large doses. In most patients doses corresponding to 200 mg. of ACTH given intramuscularly per day are given, but in severe cases 300 mg. a day is administered during the first week or two. After this initial course treatment is withheld until the disease becomes active again. Subsequent courses are given before the patient has relapsed severely; therefore, these subsequent courses need not be long, — usually one to two weeks, — but it is important that large doses be given again.

A total of 13 patients with pemphigus have been treated.[11, 12] Eight had pemphigus vulgaris, 4 pemphigus foliaceus and 1 pemphigus vegetans. All 13 are alive and in good general condition. Eight patients are, at present, free or nearly free of lesions; 2 have only a few lesions not requiring retreatment at present; and 3 are being retreated.

Chronic idiopathic generalized exfoliative dermatitis. Response to treatment is good. Often relatively small doses, that is, 100 mg. of ACTH given intramuscularly per day, appear to be adequate. After discontinuance of therapy the patient gradually relapses.

Of 2 patients treated, 1 patient received 2 courses and 1 patient 1 course of treatment. In both patients improvement was satisfactory and persisted to some degree for many months after discontinuance of treatment.

Acute Self-Limited Inflammatory Dermatoses in Which a Short Course of ACTH or Cortisone Is Indicated if the Symptoms Are Severe Enough

Drug eruptions. Drug eruptions, caused by allergy to internally administered drugs, may be severe and may even threaten life. ACTH or cortisone brings about rapid relief of symptoms. Often relatively small doses, 100 mg. of ACTH given intramuscularly per day or less, are sufficient. The length of treatment depends on the type and the severity of the eruption.

One patient with severe urticaria and fever due to allergy to parenterally administered penicillin showed great improvement after two days of treatment with ACTH. Discontinuance of treatment on the sixth day was followed by a recurrence of symptoms on the next day. After four additional days of treatment only a few urticarial lesions appeared during subsequent weeks. Another patient with a severe extensive dermatitis following injections of gold sodium thiosulfate improved within two days when treated with ACTH. After three weeks of treatment the patient was almost entirely free of lesions. No recurrence followed discontinuance of therapy.

Erythema multiforme. This disorder responds well to ACTH or cortisone. Treatment may be indicated in severe cases, particularly in those showing extensive involvement of the mucous membranes, the so-called Stevens–Johnson syndrome.

One patient with severe, frequently relapsing erythema multiforme received on two occasions a week's course of ACTH, 100 mg. a day given intramuscularly, with prompt response each time. However, the patient has since had new attacks. Another patient with severe erythema multiforme responded well and has had no further attacks.

Anaphylactoid purpura. Since anaphylactoid purpura (also called purpura simplex and Schoenlein–Henoch purpura), is an allergic disease, response to ACTH or cortisone is good, with the exception of the nephritis that is a predominant symptom in some cases.

One patient[13] with anaphylactoid purpura, arthritis and moderately severe glomerulonephritis received treatment with ACTH. The cutaneous lesions cleared, but the nephritis did not improve, despite daily administration of ACTH for nine weeks.

Contact dermatitis. In contact dermatitis it is, of course, most important to identify the responsible allergen. If this is found and eliminated, only symptomatic treatment is usually necessary. In severe cases in which the eruption is spreading,

it may be justifiable to give a short course of ACTH or cortisone in order to shorten the period of discomfort. One hundred mg. of ACTH given intramuscularly per day, — often less, — is adequate. As the treatment takes effect the eruption ceases to spread, erythema and edema decrease and itching diminishes. However, the bullae of contact dermatitis, as seen, for instance, in poison-ivy dermatitis, do not seem to involute any faster than they normally would.

One patient with extensive contact dermatitis and sensitization eruption due to application of penicillin ointment to a stasis dermatitis showed improvement within two days of treatment and was free of the eruption caused by penicillin within a week. There was no recurrence after discontinuance of therapy. The stasis dermatitis showed slight temporary improvement. Another patient with severe contact dermatitis caused by poison ivy showed no further spreading of the lesions after treatment was started. The edema diminished, but the bullae did not involute any faster than one would have expected them to do spontaneously.

Chronic, Usually Not Serious Dermatoses in Which ACTH or Cortisone Is Indicated Only in Exceptional Cases

Psoriasis. Although psoriasis responds to treatment with ACTH or cortisone, the use of these drugs is generally not advisable, as relapse occurs quickly, — often within a few days. Furthermore, it seems that not infrequently the disease is more severe in the relapse than it was prior to institution of therapy. Large doses are required in most patients with severe psoriasis. It is interesting that in patients with severe exfoliative psoriasis and rheumatoid arthritis the arthritis is likely to respond to the customary intramuscular doses of 100 mg. of ACTH per day, whereas the psoriasis may require as much as 300 mg. before it begins to improve. It is recommended to limit at present the use of ACTH and cortisone in psoriasis to patients in whom the eruption is so severe as to make the patient a bedridden invalid.

Three patients with severe generalized exfoliative psoriasis were treated.[1, 5] Two of them had a considerable degree of rheumatoid arthritis. In these 2 patients the psoriasis responded only partially even to large intramuscular doses of 300 mg. of ACTH per day, and relapse came quickly. The rheumatoid arthritis responded much better, but it also recurred gradually after discontinuance of therapy. In the third patient response to treatment with doses corresponding to 100 to 200 mg. of ACTH given intramuscularly was satisfactory, but relapses occurred within a short time after each of several courses. However, when this patient, after having received daily intravenous infusions of 20 mg. of ACTH for fourteen days, was placed on two intravenous infusions of 20 mg. of ACTH per week the eruption was held well under control.

In 6 patients with localized discoid psoriasis response was good to average intramuscular doses of 100 mg. of ACTH, but in all the eruption recurred within a few weeks after discontinuance of treatment. One patient with extensive discoid psoriasis received, after a two-week course of daily therapy, prolonged maintenance therapy consisting of small oral doses of cortisone, 75 to 100 mg. a day. In this way the psoriasis has been kept fairly well under control.

Atopic eczema. In atopic eczema the response to average doses of ACTH or cortisone is good, but from the limited experience gathered so far it seems that in atopic eczema the rebound of the disease after discontinuance of therapy is worse than in most other diseases. For this reason only very severe cases of atopic eczema should be thus treated at present; once treatment has been started one must be prepared to continue it for a long period of time.

In one patient, an adult, treatment resulted on two occasions in remarkable improvement, but on each occasion the eczema flared up severely within a few days after discontinuance of therapy. In the other patient, a one-year-old child with generalized atopic erythroderma, response to treatment was also excellent, but on discontinuance the disease relapsed, pneumonia and bilateral otitis media developed and the child died.

Chronic discoid lupus erythematosus. Although chronic discoid lupus erythematosus is basically the same disease as acute systemic lupus erythematosus, the two differ so much in their clinical course and prognosis that it is advisable to deal with them separately as far as therapy is concerned. In chronic discoid lupus erythematosus response to average doses of ACTH or cortisone is good, but, because of the temporary nature of the improvement, treatment with these drugs does not seem to be indicated except in patients with extensive lesions or considerable disfigurement. Once started, treatment must be continued for a long time. On discontinuance the eruption may become more severe than prior to treatment.

Three patients with chronic discoid lupus erythematosus were treated with ACTH. One, with extensive lesions on face, trunk and extremities, showed excellent improvement, but two weeks after discontinuance of therapy the eruption had recurred. Two patients in whom the lesions were limited to the face showed almost complete clearing of the lesions, but the disease relapsed with more lesions than had been present before treatment. In one of the patients lesions appeared even on the trunk; however, they involuted spontaneously after a few weeks.

Dermatitis herpetiformis. ACTH and cortisone are capable of suppressing this disease temporarily.

One patient with severe dermatitis herpetiformis received one course of cortisone and one of ACTH. Each time the eruption cleared, — but only with doses amounting to 400 mg. of cortisone and 300 mg. of ACTH given intramuscularly a day, respectively. After each course relapse occurred within three to four weeks.

Sarcoidosis. Considerable temporary improvement can be induced in sarcoidosis by treatment with ACTH or cortisone.

One patient[1] with cutaneous and extensive pulmonary lesions showed almost complete clearing of the cutaneous lesions and a considerable decrease in the amount of pulmonary infiltration after fifteen days of treatment with ACTH, 20 mg. intravenously per day. Four weeks after discontinuance of therapy the cutaneous lesions had not recurred, but the pulmonary infiltrate had again greatly extended.

Chronic, Serious Dermatoses in Which ACTH or Cortisone Is of Little Value

Scleroderma. In scleroderma an early inflammatory and a late fibrotic stage exist. ACTH and cortisone exert a beneficial though temporary effect on the early inflammatory lesions; on the other hand, response of the fibrotic lesions in advanced cases is only slight. Because of the extreme chronicity of the disease any temporary improvement gained by means of these drugs does not materially alter the ultimate outcome of the disease.

Six patients with systemic scleroderma were treated.[14] There was temporary slight improvement in all. Three of the 6 patients have since died of their disease. The greatest improvement was obtained in a young woman with early scleroderma who received 80 to 160 mg. of ACTH per day intramuscularly for six weeks. After this the symptoms of the disease have been partially controlled by daily intramuscular injections of 40 mg. of ACTH.

Mycosis fungoides. Mycosis fungoides is a form of lymphoma affecting primarily and predominantly the skin. The erythematous lesions respond well to treatment with ACTH or cortisone, with considerable relief of itching. The tumors show less response. Since, however, the beneficial effect is temporary, the long-range value of this treatment in mycosis fungoides is questionable.

One patient with advanced mycosis fungoides received 2 courses of treatment with ACTH. After each course improvement of the erythematous lesions and amelioration of itching were considerable. The tumors, however, did not diminish materially in size. Within two weeks after discontinuance of therapy the patient was in the same condition as he had been before treatment had been started.

Conclusions

ACTH and cortisone are of considerable value in the treatment of several serious dermatoses, such as pemphigus, systemic lupus erythematosus, dermatomyositis and generalized exfoliative dermatitis. In these diseases ACTH and cortisone represent the best treatment available and may save the life of the patient. Treatment should be started as soon as possible.

In chronic inflammatory nonfatal dermatoses, ACTH and cortisone should be administered at present only to patients who are so ill that they are bedridden. The reason for this is the temporary nature of the beneficial effect produced by ACTH or cortisone. Once started, this treatment must be carried out for a long period of time. In patients who are not seriously ill the not infrequent occurrence of undesirable side-effects on prolonged treatment may result in a situation in which the treatment is worse than the disease.

Some diseases, especially atopic eczema, psoriasis and chronic discoid lupus erythematosus, have a tendency to rebound so forcefully that the disease may be worse on discontinuance of therapy than it had been before.

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TREATMENT OF ACUTE THYROIDITIS WITH ANTITHYROID DRUGS*

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WE have treated 3 patients with acute thyroiditis, all women between forty-two and fifty-one years of age, with antithyroid drugs, with prompt resolution of the disturbance in all. Two additional patients, aged fifty-five and forty-eight, who presented suggestive signs of acute thyroiditis and responded to treatment with thiouracil, are not included in this report because the diagnosis was not so clear-cut as in the others. One of them had a Hashimoto-struma lymphomatosa with a flare-up simulating acute thyroiditis. The other presented comparatively few distinctive symptoms of this disease but showed more evidence of an acute hyperthyroidism.

Acute thyroiditis is a self-limited disease of unknown etiology occurring relatively infrequently and attacking mostly women with or without goiter. Approximately half the attacks follow an acute upper-respiratory infection. In some it may appear in combination with a wide variety of acute infectious processes, but in others there seems to have been no previous illness. The onset is sudden, and the patient often has difficulty in localizing the source of the trouble. Pains appear in the front or sides of the neck, in the ears or in the temporomandibular joints. Chills, fever, malaise and dysphagia often occur, and painful swelling and tenderness develop over the thyroid gland. This swelling is diffuse and firm, and the overlying skin may be red. Resolution takes place after from one to several weeks. The pains stop; the inflammatory process and the swelling recede. The tenderness disappears more gradually. In most patients recovery is usually complete, with no apparent damage to the gland and no systemic disturbance.

In the detailed report that follows the similarity may be noted between the course of the disease in our patients and the general pattern described above. Of particular interest is the development in one patient of a severe secondary anemia during the acute stage with the appearance of frank myxedema three months after recovery.

CASE REPORTS

CASE 1. Mrs. R. B., a 51-year-old woman, noted tenderness and swelling over the right lobe of the thyroid gland on July 11, 1945, shortly after the extraction of 8 teeth. She developed increasing fatigue as this condition persisted. Lugol's solution was prescribed by her physician and had been taken for 5 weeks, from August 25 to October 22, when she was first seen.

On September 11 the left lobe of the thyroid gland also became painful and began to enlarge. Fatigue and malaise increased and nervousness and palpitation appeared. The basal metabolic rate on September 1 was +1.

On physical examination the thyroid gland showed tenderness and smooth bilateral enlargement. The patient had difficulty in swallowing and pain on extending her neck. The temperature was 98°F., the pulse rate 108. All medication was stopped and she was given thiouracil, 0.1 gm. three times a day. Little improvement occurred during the next 10 days and, because the patient complained of a sore throat, the thiouracil was discontinued. It was resumed after 3 days, as there was no fever and no change in the blood count. The pain and tenderness over the thyroid gland had begun to diminish on the eleventh day of treatment, and the gland was smaller on the next day. Improvement continued from this point on, and the thyroid was back to normal size by October 28. The basal metabolic rate was now −3, and the blood count was normal. Thiouracil was continued for another 4 weeks and then stopped. The patient recovered fully, and the thyroid was barely palpable. Subsequent re-examination at frequent intervals has disclosed no abnormalities, and the patient has maintained good health.

Comment. In this case, the inflammation followed the extraction of some teeth, involving first the right and then the left lobe of the thyroid gland during a period of 9 weeks. Lugol's solution was of no help during the 5 weeks it was given and may have delayed the action of the thiouracil. Improvement followed after 12 days' treatment with thiouracil and proceeded to complete recovery without sequelae.

CASE 2. Mrs. M. L., a 48-year-old woman, was first seen on April 10, 1950, because of fever, malaise, weight loss and pain, tenderness and enlargement of the neck at the thyroid region. Her illness had begun 5 weeks previously, with what was described as an "enlarged gland" in the left side of the neck. Three weeks later she had a temperature of 101°F. daily, and the pain and swelling over the thyroid gland had increased. Penicillin and Chloromycetin were used without effect.

On physical examination the thyroid gland was tense and tender, nodular and enlarged throughout. Part of the gland was retrosternal. The temperature was 100.2°F., the pulse rate 72 and the blood pressure 122/50. The basal metabolic rate was +1. Examination of the blood revealed a hemoglobin of 66 per cent, a red-cell count of 3,340,000 and a white-cell count of 8700, with 77 per cent neutrophils. The sedimentation rate was 45 mm. in 1 hour (Westergren).

The patient was started on 5 mg. of Tapazol (1-methyl-2-mercaptoimidazole) 3 times daily, which was continued for 12 days before the pain and tenderness stopped. During this time the fever continued, and the patient was distressed by choking and difficulty in swallowing. On the first day of improvement the thyroid gland was still enlarged and very hard. The basal metabolic rate was +8. The Tapazol dose was reduced to 5 mg. daily. The blood count now showed a hemoglobin of 49 per cent, with 3,080,000 red cells and 6500 white cells, with 76 per cent neutrophils. Blood cultures were negative, and a bone-marrow study showed only a secondary "toxic" anemia.

Improvement continued from this point on and the Tapazol was stopped on April 27, when the basal metabolic rate was −7. Ferrous sulfate was given, and the patient was discharged from the hospital on May 11. Five days later the basal metabolic rate was −22, the hemoglobin 59 per cent and the red-cell count 3,860,000. The thyroid was painless, firm and smaller, and the patient's only complaint

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was of continuing fatigue. The condition of the blood improved slowly from this point on, and the thyroid gland diminished in size so that by June 7 it was barely palpable. The fatigue had improved but little. When the patient was seen on August 22, 12 weeks after discharge from the hospital, she presented a changed appearance, highly suggestive of myxedema. Her fatigue had continued, the skin was dry and the face puffed, particularly about the eyes, and she was quite untroubled by the hot weather. The basal metabolic rate was −19, the hemoglobin 71 per cent and the red-cell count 3,910,000. Thirty mg. of thyroid was given, and improvement followed during the next 4 weeks. The dose was then doubled, with continued good effect, and gradually increased to the present level of 0.12 gm. daily. On January 3, 1951, the basal metabolic rate was −12, the weight had increased by 7 pounds; the hemoglobin was 74 per cent and the red-cell count 4,080,000. The thyroid gland was no longer palpable and the patient was in good health.

Comment. This patient had acute thyroiditis of undetermined origin for five weeks during which there was no response to antibiotics. Twelve days after starting treatment with Tapazol, resolution appeared, with rapid improvement from then on. A progressive secondary anemia developed during the course of the illness and the fatigue continued after the acute phase had subsided. Three months afterwards she developed myxedema, most likely a complication of the inflammatory process. The patient is now maintaining good health with the aid of thyroid substance.

Case 3. Mrs. C. P., a 42-year-old woman, was first seen on December 18, 1950, because of persistent pain in the right temporomandibular joint that radiated into the right side of the neck. She had consulted her dentist, but he could find no cause for the pain. Her temperature was normal and her pulse rate was 116. A moderately tender area in the region of the right thyroid lobe was noted, but no significance was attached to this finding. She was referred to an oral surgeon, who treated the temporomandibular arthritis with locally injected procaine. Some relief was obtained, but the pain persisted and spread to the left side of the neck and then to the left temporomandibular joint. She was referred back to us on January 13, 1951, complaining of increasing pain now definitely referred to the thyroid region. The temperature and pulse were normal, there was a fine tremor and the palms were warm and moist. The thyroid gland was hard, slightly more enlarged on the left than on the right and extremely tender to touch. The patient complained of pain on extending the neck and some difficulty in swallowing.

She was given 5 mg. of Tapazol twice daily, and ice was applied over the thyroid gland. The cold was not tolerated, and codeine had to be given to control the severe and increasing pain. Swallowing became more difficult, and choking occurred when the patient lay flat or on one pillow. The condition worsened steadily during the next week as the thyroid gland increased in size, and the left lobe and isthmus became prominent, hard and extremely tender. There was no fever.

On January 18 the basal metabolic rate was +10. Examination of the blood showed a hemoglobin of 73 per cent, a red-cell count of 3,810,000 and a white-cell count of 11,100, with 62 per cent polymorphonuclear leukocytes. The sedimentation rate was 85 mm. in 1 hour (Westergren). On January 22 the white-cell count was 18,400, with 70 per cent polymorphonuclear leukocytes. The following day the pain diminished somewhat and in another 24 hours improvement was noticeable. The pain, dysphagia and choking had lessened, and the gland was a little smaller and less tender. On January 27 the basal metabolic rate was −2, but the white-cell count was still 17,200 with 87 per cent neutrophils. The sedimentation rate was now 31 mm. in 1 hour.

Improvement continued, with rapid reduction in the thyroid enlargement. The Tapazol was discontinued on February 1, at which time the basal metabolic rate was −8, the hemoglobin 73 per cent, the red-cell count 4,300,000 and the white-cell count 10,700, with 71 per cent polymorphonuclear leukocytes. The patient was entirely symptom-free. The thyroid was much smaller, but both lobes were still palpable and quite hard. She has continued in good health without complications.

Comment. In this case are exemplified the vague nature of the initial symptoms in acute thyroiditis and the absence of antecedent causative factors. The illness was present for four weeks before it was recognized. Fever was absent and evidence of thyrotoxicosis was minimal. Leukocytosis developed late. Resolution appeared nine days after starting therapy with Tapazol. Recovery followed without complications.

Discussion

Although no large series of cases of acute thyroiditis has been reported by any one author, the condition has been recognized for many years and discussed, however briefly, in most medical texts. Kocher[1] observed that most forms of acute thyroiditis are secondary to acute infection elsewhere in the body, the organisms reaching the thyroid through the blood or lymph stream or, occasionally, by extension from the larynx or trachea and, rarely, by way of a persistent thyroglossal duct.

Crotti[2] claims that there is no such entity as a primary infection of the thyroid and that the bacterial nonsuppurative form is only a phase of a process whose last act is suppuration. In his experience the temperature is often low and the pulse high (of thyrotoxic origin).

DeCourcy[3] notes that the goitrous gland is far more susceptible to acute inflammatory reaction than is the normal gland. There is justification in assuming a bacterial origin for most cases, even though bacterial findings have been rare. No particular type of organism appears to be etiologically significant, and often no other infection, local or systemic, has preceded the attack.

Means[4] has never seen acute thyroiditis develop in the course of toxic goiter or in a thyroid gland that was the seat of disease but adds that this is not impossible. When developing in a previously normal gland the process is a diffuse one, whereas in nodular goiter it may be confined to a single nodule.

Pathologically, the changes, according to Crile,[5] consist of a diffuse involvement of the entire thyroid gland in a subacute inflammatory process, with leukocytic infiltration and the appearance of numerous foreign-body giant cells. The arrangement in pseudotubercular form is responsible for the condition's being termed "pseudotuberculous thyroiditis." The glands are not over two or three times normal size, the enlargement is symmetrical and the cut surface is white and avascular. The capsule is only lightly adherent to surrounding structures.

DeCourcy[3] also describes the inflammation as being confined within the capsule, although this may be involved to such an extent that the gland be-

comes fixed to adjacent structures. Edema is marked. He notes certain resemblances in some to the leukocytic infiltration characteristic of struma lymphomatosa. In others a fibrosis may develop. The connective tissue may be edematous, the colloid is absent or pale and the acinar epithelium may have undergone disarrangement and degeneration. Interspersed among the areas of fibrosis, polymorphonuclear infiltration and early or late acinar degeneration are areas of normal or nearly normal parenchyma.

Clinically, there is general agreement among all observers concerning the higher incidence in females and the general clinical picture as it unfolds. Some difference of opinion exists concerning whether the symptoms simulating those of hyperthyroidism are actually due to hyperfunction of the gland or to the general toxemia. Crotti[2] attributes the rapid pulse with low temperature to thyrotoxicosis, whereas Crile[5] thinks that this is not true hyperthyroidism and DeCourcy[3] believes that the acute inflammation may give rise to constitutional symptoms suggesting thyrotoxicosis and permitting an erroneous diagnosis of hyperthyroidism. Means[4] maintains that neither hypothyroidism nor hyperthyroidism is produced, the function of the gland remaining unmolested. Duncan[6] finds the condition almost never associated with hyperthyroidism. McCombs[7] is of the same opinion, but Stevens[8] reports symptoms of hyperthyroidism in some instances. King and Rosellini[9] liken the disease to mild hyperthyroidism, for which it may easily be mistaken.

The general opinion, then, is that the condition is not accompanied by a true hyperthyroidism. This would explain the failure of iodine to be of help and raises doubt of the therapeutic value of the antithyroid drugs.

As to treatment, Means[4] recommends no special method, since in his experience the disease generally resolves in a few days. Crile[5] states that although the course of the disease tends toward spontaneous recovery it may be shortened by thyroidectomy or x-ray therapy or, possibly, by treatment with thiouracil. He finds that the condition responds promptly and completely to x-ray therapy. King and Rosellini[9] tried iodine, rest, hot applications, ice bags, the sulfonamides and x-ray therapy. They found the latter the only therapeutic agent that seemed to shorten the course of the disease, but a discouraging percentage of their cases are followed by varying degrees of hypothyroidism or myxedema. Their original use of thiouracil, with termination of the treatment at the end of a week in 8 patients who had the disease for no longer than three weeks, seemed most promising and worthy of trial. However, few evaluations have appeared in the literature.

Complications occur infrequently, but Crile, Sr.,[10] Stevens,[8] Osler[11] McCarrison,[12] DeCourcy[3] and McCombs[7] observed that myxedema may follow, and Hertzler[13] warns that abscess may form late, particularly in the aged and feeble. This risk is probably minimal now that the antibiotics are available.

Only one of our patients (Case 1) gave a history that linked the acute process to a preceding cause. One patient (Case 2) developed a severe secondary anemia during the course of the disease, and myxedema appeared three months after recovery. All of our patients responded to antithyroid therapy, the first 2 in twelve days and the third in nine days. It is recognized that treatment was not started until the disease had been in existence for varying periods of time, when resolution might have been already under way.

Summary

The patient with acute thyroiditis is generally a middle-aged woman with or without goiter who may or may not have had an antecedent infection. The disease begins with vague symptoms not always immediately localized in the thyroid gland. There is low-grade fever, with malaise, and pains about the neck, jaws and ears. The pain gradually localizes at the thyroid gland, which becomes swollen and tender. Extension of the head is painful and dysphagia increases. Symptoms suggestive of hyperthyroidism often appear. This process may develop during several days to weeks and may resolve spontaneously within a few days.

Operation is rarely indicated. X-ray therapy seems to be of help, but it introduces the risk of subsequent myxedema. Iodine, heat, cold and the antibiotics exert no favorable influence.

The antithyroid drugs appear to be helpful and deserve a trial.

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MEDICAL PROGRESS

BLOOD GROUPING, BLOOD BANKING AND BLOOD TRANSFUSION*

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HISTORICALLY, transfusion therapy is no longer an infant but a vigorous youth. Certain of its phases have already acquired definite shape, based on accumulated experience, from which little immediate change is to be anticipated. Others, particularly those involving laboratory methodology, the fractionation of donor blood and the preservation of its separated elements, are still subject to extensive modification with the expectation that many concepts and practices now current will presently be outmoded. The authors of this paper have attempted to recapitulate and summarize the more recent advances in blood banking and blood-transfusion therapy, limiting their discussion to material that is of practical importance and of immediate concern and which, for the most part, has already gained general acceptance.

THE BLOOD-GROUP ANTIGENS

The red blood cells of every human being contain many different blood-group substances.[1] Of the well known blood-group substances to be described in the following paragraphs, at least 6 must be present in the red blood cells of every person; the maximum number possible is 19, and the average number is about 12. These blood-group substances are divided into 9 "systems" (Table 1), the basis of this division being that the blood-group substances in each of these 9 systems are inherited independently of those of each of the other systems.

The blood-group substances are complex chemical compounds. Only those of the ABO system have been extensively studied from the chemical viewpoint. These are complex polysaccharides, chemically indistinguishable from each other by present methods, though very different immunologically. The rather meager evidence indicates that they are present in patches on the surface of the red blood cell and that the patches of Rh substance are in a different location from the patches of A, B or O substance and so forth.

Individual blood-group substances vary in antigenicity. Some, like A, B and D (Rh_o), are effective antigens, but only in those human beings who lack them. Others, like O, N and P, are very weak antigens. Others are intermediate in antigenicity. The clinical importance of the various blood-group substances is determined principally by their antigenicity, since a person who lacks a particular blood-group antigen in the red blood cells is liable to immunization (sensitization) by that antigen if exposed to it by parenteral injection of the antigen in the form of whole blood or by transplacental transfer. The immunization of human beings to substances of human origin (such as the blood-group antigens) is called isoimmunization (isosensitization). Because of their greater antigenicity, A, B and D are the most frequent isosensitizing antigens, and they are therefore of greatest clinical importance.

THE BLOOD-GROUP ANTIBODIES

Human blood-group antibodies (isoantibodies) are, principally, globulins. They are found in the blood serum of most human beings in various numbers and combinations. Only persons of Group AB are likely to have no blood-group isoantibodies of any kind. These antibodies serve no useful purpose to the person who possesses them but do constitute a hazard to the individual, and a potential hazard to the babies of women who possess them. They are a bother to the physician faced with the necessity of giving blood transfusions or treating babies with erythroblastosis fetalis, and they have become a specialty in medicine for those whose business is the operation of blood banks and blood-grouping laboratories or the production of typing serums.

Until the discovery of the Rh blood groups, only five human blood-group antibodies were generally recognized. These were anti-A, anti-B, anti-M, anti-N and anti-P. The first two were obtainable either from human or from animal sources; the latter three were usually obtained from animals (after immunization with human blood of suitable type). In the ten years since the discovery of the Rh blood groups, not only have a large number of other specific isoantibodies been discovered, but it has been shown that isoantibodies of any particular specificity may exist in different forms. Anti-D (anti-Rh_o), for example, has been found in at least three different forms, designated by a variety of terms. These terms are listed in Table 2, the various designations in each column being synonymous. The terms used at the top of each column are those

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that are perhaps least likely to be misunderstood, since they refer to the type of test used in the laboratory for the detection of the various forms of antibody. Antibodies of the first variety, the saline-active antibodies, may cause hemolytic transfusion reactions but do not usually cause erythroblastosis fetalis, because they ordinarily fail to pass through the placenta from mother to fetus. Albumin-active and blocking antibodies may cause erythroblastosis fetalis as well as hemolytic transfusion reactions. All three varieties of anti-D may coexist in the same serum, and when this occurs the presence of one may mask the presence of another. For example, a high-titered saline-active antibody makes the detection of a coexisting lower-titered albumin-active antibody impossible by ordinary laboratory methods. There are important physicochemical differences among the different varieties of anti-D.

In addition to containing more than one variety of a particular specific antibody, a human serum may, and not infrequently does, contain a number of antibodies of different specificity. Anti-A, anti-B, anti-C (Rh′) and anti-D (Rh_0) are found simultaneously in a fair number of serums from women who are Group O, Rh-negative. Anti-Kell has been found in other serums in addition to the other four. In one carefully examined serum, from a repeatedly transfused patient, nine different specific blood-group isoantibodies were found simultaneously. Thus, the detection of isoantibodies of one specificity does not rule out the presence of antibodies of another specificity, and the positive identification of a particular antibody requires careful selection of test bloods. Furthermore, the demonstration that a serum does not contain antibodies of one specificity is no guarantee that other important isoantibodies may not be present.

TABLE 1. *Principal Genes and Antigens of the Nine Important Blood-Group Systems.*

SYSTEM	I* ANTIGENS THAT HAVE CAUSED ERYTHROBLASTOSIS FETALIS AND MAY CAUSE HEMOLYTIC TRANSFUSION REACTIONS	FREQUENCY OF MATINGS IN WHICH HUSBAND'S BLOOD IS INCOMPATIBLE WITH WIFE'S BLOOD	APPROXIMATE FREQUENCY OF ERYTHROBLASTOSIS FETALIS	II* ADDITIONAL ANTIGENS THAT MAY CAUSE HEMOLYTIC TRANSFUSION REACTIONS†	FREQUENCY OF TRANSFUSIONS IN WHICH DONOR IS INCOMPATIBLE WITH RECIPIENT IN RESPECT TO ANTIGENS IN COLUMNS I AND II, IF THEY ARE MATCHED FOR A, B, AND D	III* ANTIGENS THAT HAVE NOT CAUSED ERYTHROBLASTOSIS FETALIS OR HEMOLYTIC TRANSFUSION REACTION	IV OTHER BLOOD-GROUP GENES WHOSE EXISTENCE IS ASSUMED
			per 1000 births				
ABO System	A (.45)‡ B (.14)‡	.35	0.6			O(.885)	
Rh System	C (.70) c (.80)	.37	>0.1		.23		d (.63)
	D (.85)	.13	6				
	E (.30)	.21	>0.1	e (.97)	.18		
				M (.79)	.17	N (.72)	
MNS System ...				S (.57)	.35		
	s (.88)	.10	>0.1		.09		
Kell System	K (.10) k (.998)	.09	0.1				
Duffy System				Fy^a (.65)	.23		Fy^b (.83)
Kidd System				Jk^a (.77)	.18		Jk^b (.73)
P System						P (.71)	p (.79)
Lewis System						Le^a (.68) Le^b (.75)	Le^c (.14)
Lutheran System						Lu^a (.08)	Lu^b (.998)

*These antigens are identifiable with typing serums.
Genes (antigens) shown in same horizontal line are mendelian alleles.
The Rh System involves 3 linked genes. The MNS System involves 2 linked genes.
†Presumably any of these might cause erythroblastosis fetalis.
‡Frequencies in parentheses = for white population.

TABLE 2. *Forms of Anti-D (Anti-Rh_0).*

"Saline-active" antibodies	"Albumin-active" antibodies	Blocking antibodies*
Complete antibodies	Incomplete antibodies	
Agglutinins	Glutinins	
Early immune antibodies	Late immune antibodies	
	Hyperimmune antibodies	
	"Blocking" antibodies*	
	"Blockers"*	Blockers
	Cryptagglutinoids	

*The term "blocking" antibodies, although frequently used to designate albumin-active antibodies, is not properly used thus. Serums containing albumin-active antibodies not infrequently contain blocking antibodies also, but often do not.

THE A-B-O BLOOD GROUPS

The A-B-O blood group of a person depends on a pair of genes. Since there are three (disregarding the variant A_3) alternative (allelic) genes, designated A, B and O, there are six possible genotypes, or gene pairs, designated AA, AB, AO, BB, BO and OO. Table 3 summarizes the typing reactions of these 6 genotypes. The phenotype is the group determinable by typing tests, and it is seen that the

TABLE 3. *ABO Blood Groups.*

GENOTYPE (GENE PAIRS; ALSO, ANTIGENS PRESENT IN RED CELLS)	GROUP (PHENOTYPE)	REACTIONS OF CELLS WITH TYPING SERUMS: ANTI-A	ANTI-B	ISOANTIBODIES IN SERUM
AA	A	Positive*	Negative†	Anti-B
AO				
BB	B	Negative	Positive	Anti-A
BO				
AB	AB	Positive	Positive	—
OO	O	Negative	Negative	Anti-A and anti-B

*Positive = cells agglutinated by antiserum in question.
†Negative = cells not agglutinated by antiserum in question.

phenotype (group). A includes the genotypes AA and AO, which are at present indistinguishable by typing tests. It is to be noted that anti-O typing serum is not used in typing tests for ABO blood group. This is because anti-O serums that distinguish the genotypes AA and AO are exceedingly rare, presumably because O is a very weak antigen in human beings.

Anti-A is found in all persons (with very rare exceptions) whose cells lack the A antigen, anti-B in all (with rare exceptions) whose cells lack the B antigen, except in many newborn babies. This also is summarized in Table 3. It is impossible satisfactorily to account for the presence of these antibodies on a genetic basis. They are generally spoken of as "natural" antibodies, although it is likely that they are actually acquired antibodies, acquired quite possibly as a result of ingestion or inhalation of the antigen.

Anti-A and anti-B are usually of the saline-active variety (see Column 1, Table 2). Another variety is recognizable, in the serum of some persons, corresponding in general to the variety of antibody in Column 2, Table 2, but requiring a somewhat different diluent from bovine albumin for its in-vitro demonstration (human serum, acacia solutions and so forth). These serum-active anti-A and anti-B antibodies are responsible for approximately 10 per cent of cases of erythroblastosis fetalis and for some cases of hemolytic transfusion reactions when "universal" donors are used. Their presence in any particular human serum may be the result more of a peculiarity in the antibody-producing mechanism of the person than of the type of antigenic stimulus.

The RH (C-D-E) Blood Groups

The Rh blood groups are more numerous than the A-B-O blood groups because there are, according to Fisher's theory, three pairs of closely linked genes involved in their inheritance, with at least two alleles for each pair. Thus, not counting any of the variants, there are 36 possible genotypes in the Rh system. When combined with the 6 genotypes in the A-B-O system, they make 216 genetically different types, based on these two blood-group systems alone.

Of the various antigens in the Rh system, D (Rh_o) is by far the strongest, and therefore of greatest clinical importance. The relative weakness of the others, c (Hr'), E (Rh''), C (Rh'), e (Hr'') and d (Hr_o) (in approximately that order of descending antigenic potency), is such that they are of much less importance clinically. To say that a person is Rh-negative means, or should mean, that he is D-negative, whether or not he is C-positive or E-positive.

One of the variants in the Rh system of blood-group substances is important enough for special comment. This is the variant commonly called D^u. Unfortunately, it is not a single specific blood-group substance that can be identified by a specific typing serum, but rather a large group of variants, very closely related to D (Rh_o) and distinguishable from D only by quantitative methods. Its importance lies in the fact that, from the point of view of typing tests, it is weaker than ordinary D and thus not so easily recognized, whereas on the other hand it not only is antigenic (causing the production of *ordinary anti-D* in the Rh-negative recipient) but may be the cause of fatal hemolytic transfusion reaction if the recipient is already sensitized to D. Approximately 1 per cent of the white race (a much higher percentage of Negroes) are of the type called "D^u." This means that approximately 6 per cent of supposedly Rh-negative donors would actually be Rh-positive if all the D^us went unrecognized. Fortunately, as Rh typing serums have improved, the percentage of these persons typed correctly as "Rh-positive" has steadily increased. They are more likely to be recognized correctly if more than one anti-D serum is used. The best safeguard is the use of the indirect Coombs test in conjunction with a high-titered anti-D to retest all supposedly "Rh-negative" donors. The D^u variants are genetically related to D as alleles and are serologically unrecognizable in the presence of ordinary D. These facts are summarized in Table 4.

Table 4. *Reactions of Red Cells of Various Persons with Anti-D Serums.*

Genotype	Weak Anti-D	Strong Anti-D with Indirect Coombs Test	Phenotype
DD	Positive*	Positive	Rh-positive
Dd	Positive	Positive	Rh-positive
dd	Negative†	Negative	Rh-negative
DD^u	Positive	Positive	Rh-positive
D^ud	Negative	Positive	Rh-positive (D^u variant)

*Positive = agglutination with designated serum.
†Negative = no agglutination with designated serum.

Anti-D (anti-Rh_o) is the blood-group isoantibody most commonly responsible for erythroblastosis fetalis (about 90 per cent of cases), and, next to anti-A and anti-B, most commonly responsible for hemolytic transfusion reactions. The various forms of anti-D have been discussed. Methods of detecting anti-D in human serums will be discussed in the section on technics.

The M-N-S Blood Groups

The blood-group substances M, N, S and s are genetically unrelated to the A-B-O or Rh blood-group substances. M and N are allelic. S and s are closely linked genetically to M and N (as E and e are related to C and c). M and N are weak antigens, — especially N, only rare cases of clinical difficulties having been recorded as attributable to anti-M. S is a stronger antigen than M or N and has been associated with transfusion reactions and erythro-

blastosis fetalis; s has been found in the serum of a woman whose baby had erythroblastosis fetalis.[2]

Anti-M and anti-N, when found in rare human serums, have been of the saline-active variety. Anti-S may be of the saline-active variety, but several examples have been found that are demonstrable only by the Coombs method.

Generally speaking, M, N, S and s are of no clinical importance; hence routine M-N-S typings are not performed for purposes of transfusion. Anti-M and anti-N typing serums are obtained by the immunization of rabbits with human blood of appropriate types. Anti-S typing serum is very scarce and has been obtained only from human donors immunized accidentally by transfusion or pregnancy. Attempts to produce anti-S in human volunteers have not been successful.

The P Blood Groups

The blood-group antigen P has been recognized since 1927, with the use of typing serum of animal origin. It is now recognized that a large percentage of P-negative persons (about 30 per cent of human beings are P-negative) have low-titered anti-P saline-active agglutinins in their serum. These agglutinins usually are active only at low temperatures (4°C.). Clinical problems associated with anti-P are exceedingly rare, and the antigen has little or no clinical importance. P is genetically unrelated to the other blood-group systems.

The "Lewis" Blood Groups

At least two immunologically distinct blood-group substances in the Lewis system have been identified. These are designated Le^a, and Le^b. The existence of a third, Le^c, has been postulated on good evidence. They are genetically unrelated to the other blood-group systems. It is generally thought that the isoantibodies of the Lewis system are of no clinical importance.

The "Kell" Blood Groups

Kell (K) and k (Cellano) are moderately antigenic substances, genetically unrelated to the other blood-group systems. In spite of the low frequency of Kell-positives in the population (less than 10 per cent), the Kell antigen (K) and antibody are probably responsible for more cases of erythroblastosis fetalis than any other blood-group antigens except D, A and B. Even so, the frequency of erythroblastosis or transfusion reactions caused by Kell is so low that routine blood typing with anti-Kell is not worth while, although abundant typing serum of human origin is available.

Anti-Kell antibodies are, more often than not, inactive in saline medium, requiring albumin or the Coombs test method for their detection. A single example of anti-k has been found, in the serum of the mother of an erythroblastotic baby, which is a saline-active agglutinin, agglutinating the red blood cells of 99.8 per cent of human beings.

The "Lutheran" Blood Groups

Only one substance has been identified in the Lutheran system. It is designated Lu^a. So far as is known, no clinical problems have arisen as a result of blood-group incompatibilities with respect to Lu^a, which is found in the red cells of less than 10 per cent of the population. Lu^a is genetically unrelated to the other blood-group systems.

Anti-Lu^a has been found in the serum of several human beings, as the result of incompatible blood transfusion (without reaction). These antibodies have invariably been saline-active agglutinins. Typing reagents of this specificity are, however, very scarce.

The "Duffy" Blood Groups

An eighth blood-group system, genetically unrelated to the others, was described in 1950. A single blood-group antigen in this system has been identified to date, designated Fy^a. Although the Fy^a substance is presumably a weak antigen, a number of hemolytic blood-transfusion reactions have resulted when Fy^a-negative persons have received multiple transfusions of Fy^a-positive blood. Frank cases of erythroblastosis fetalis have not been described, although it is possible that early fetal death occurs in the Fy^a-positive fetus of a sensitized Fy^a-negative mother.

A number of examples of anti-Fy^a have been found in this country and abroad. All share the peculiarity that their agglutinating activity is not manifest with saline or albumin suspensions of red cells but is clear-cut by the Coombs test technic. Approximately 65 per cent of human beings are Fy^a-positive.

The "Kidd" Blood Groups

A ninth blood-group system, apparently unrelated to the other eight systems, has recently been described.[3] The single blood-group antigen so far identified in the Kidd system has been designated as Jk^a. The antibody, anti-Jk^a, by means of which the new blood-group system was detected, was found, along with anti-Kell, in the serum of a woman who had delivered an erythroblastotic baby. She had not received a transfusion.

This original example of anti-Jk^a was at first a saline-active antibody, but the serum quickly lost all activity against saline-suspended red cells, now requiring the Coombs method to demonstrate the antibody-antigen combination. Approximately 77 per cent of human beings are Jk^a-positive.

Other Blood Groups

There are excellent reasons for believing that still other, genetically independent and possibly clinically important, blood-group systems exist.

It is to be hoped, from the point of view of the study of human genetics, that there are many others. Medicolegal and anthropologic investigations will be greatly aided by foreseeable advances in blood-grouping technics.

Blood-Typing Technics

There is almost no limit to the number of possible variations of blood-typing technics. In general, all depend on agglutination of the red cells of certain persons and lack of agglutination of the cells of others, by typing reagents of various specificities, under more or less rigidly controlled conditions of temperature, pH, salt concentration, protein concentration and so forth. Obviously, therefore, the technician must know the conditions under which each particular serum yields correct positive and negative results. For this reason, — and this cannot be emphasized too strongly, — whatever blood typing serum is used, *the manufacturer's directions for use should be followed in every detail.* In no other way can the results obtained be relied on. One important fact must always be kept in mind — that the typing serum may contain blood-group antibodies other than that specified on the label. If the directions of the manufacturer are followed, these other antibodies may be assumed not to interfere with the specific reaction desired. If other technics, especially the more sensitive methods, are used, unexpected results may occur, and false reports may be made.

The only deviation from manufacturer's directions that is generally allowable is the performance of the Coombs test on cells that have been exposed to anti-D without having been agglutinated. This test should not be applied to transfusion recipients, for a number of technical reasons. However, it is a recommended procedure for blood donors in order to label correctly the Rh-positive (D^u) variants among blood donors. The Coombs test serum should be used according to the directions of the manufacturer, and the anti-D serum used should be free of anti-C or anti-E.

There are a number of reliable commercial typing serums on the market. The manufacturers are licensed by the National Institutes of Health for the production and distribution of typing serums and must submit samples of each lot to the NIH for approval before marketing. This assures a minimum standard of potency, which for anti-A is a titer of 1:256 against A_1 cells, 1:128 against A_1B and A_2 cells and 1:64 against A_2B cells. For anti-B, the requirement is a titer of 1:256 against cells of group B. For anti-Rh serums it is a titer of 1:32. If a producer of typing serum holds a license from the NIH the fact will be stated on the package.

Of great importance also are some general principles that should guide the technician in performing blood-grouping tests. In addition to buying reliable serums, the cost of which is of minor importance in comparison with their reliability, it is essential to know what serums to buy. Anti-A agglutinates A_1, A_2, A_1B and A_2B red cells. It is obtained from donors of blood-group B but should not be called "Group B" serum. The use of such a designation is dangerous, because it is confusing. Anti-B serum agglutinates B, A_1B and A_2B cells and is obtained from donors of blood-group A. It should never be referred to, however, as "Group A" or "A" serum. Anti-D (anti-Rh_o) agglutinates all cells that have the D antigen and is the *only* anti-Rh serum that distinguishes "Rh-positive" persons from "Rh-negative." These are the three basic serums for routine grouping, and other serums should *never* be used for routine groupings.

Single typing tests should not be accepted as proving the blood type of the person being tested, except as an emergency procedure. Direct typings with anti-A and anti-B typing serums should be confirmed, whenever possible, by serum typings, otherwise known as "back-typings." The basis of back-typing is the fact that Group A persons have anti-B in their serum, Group B persons have anti-A, Group O persons have both anti-A and anti-B and Group AB persons have neither. Two drops of inactivated (at 56°C. for 20 minutes) serum from the person being tested are put in each of two small test tubes, the one containing a drop of 4 per cent saline suspension of cells from a known Group A_1 person, the other containing a drop of a 4 per cent saline suspension of cells from a known Group B person. Preferably, the donors of these cells are persons working regularly in the laboratory or in the hospital, so that the cells can be obtained as needed and a fresh supply (not over a week old) of blood kept on hand. If their blood is taken into citrate or oxalate solution, the aliquot taken for a day's use should be washed once with physiologic saline solution to remove fibrinogen. These donors should be Rh-negative, so that the possible presence of anti-Rh agglutinins in the serum being tested will not interfere. The tubes may be spun down immediately and examined for agglutination, the presence or absence of agglutination of the known bloods indicating the blood type of the person being tested (see Table 5).

Table 5. *Back Typing for ABO Blood Groups.*

Blood Group of Person Being Tested	Agglutination of Cells of Group A_1 by Serum of Person Being Tested	Agglutination of Cells of Group B by Serum of Person Being Tested
Group O	Positive*	Positive
Group A	Negative†	Positive
Group B	Positive	Negative
Group AB	Negative	Negative

*Positive = agglutination.
†Negative = no agglutination.

When the results of back-typing agree with the results of direct typing, the major type of the blood

being tested can be assumed to have been correctly determined. When a discrepancy is found between the two methods both should be repeated, and if the discrepancy still exists the problem of determination of the correct type is usually a difficult one, and the blood should be sent for typing to a specialized laboratory, of which there are a number in the United States.

Back-typing for confirmation of the Rh type is not possible, because so few Rh-negative persons have anti-D in their serum. (When they have it, it is an abnormal situation, resulting from previous blood transfusion or from pregnancy.) Confirmation of the original Rh typing should be sought, therefore, by testing the blood with a second Rh typing serum, preferably from a second manufacturer. It is well also to use for one of the Rh typing tests the slide test technic and for the other a tube test technic. The manufacturer usually furnishes directions for both technics in his package circular. Any discrepancy between the two tests should be investigated, first by repeating the original tests, using known Rh-positive and known Rh-negative bloods as controls. When the discrepancy cannot be resolved, the blood should be sent to a special laboratory, with samples of the serums used for testing and the details of the methods used and the results obtained. If the serums are potent and specific and the tests are made according to directions, discrepancies that cannot be easily resolved will be very uncommon.

Cross-Matching Procedures

It is not generally recognized that the cross-match test is actually the prototype of the test for blood-group antibodies in a human serum. It is, of course, a special example of an antibody test, as the cells and serum are carefully selected for compatibility by A, B and Rh testing, whereas in the ordinary test for blood-group antibodies it is customary to use a variety of cells selected so that some will be compatible and others potentially incompatible with the serum being tested. If blood-group antibodies were never present in human serums, blood typing and cross-matching would never be necessary. Actually, anti-A or anti-B, or both, are present in most serums, and the variety of other antibodies possibly present may be large. As in the ordinary test for antibodies, the important problem is to demonstrate such antibodies, if they exist in the serum of the recipient (or donor) when the corresponding blood-group antigen is present in the red cells of the donor (or recipient). It is evident, from the discussion of the various blood-group antibodies in the preceding paragraphs, that only those antibodies that are "saline-active" will be demonstrated by the standard, time-honored cross-match test that uses saline suspensions of cells, even when an incompatibility exists that would result in a hemolytic transfusion reaction. Actually, the problems in cross-matching are essentially identical with those of testing for blood-group antibodies, and the same laboratory technics are valuable in both situations. These technics involve the use of bovine or human albumin, human serum, special temperatures, trypsinization of the red cells and the Coombs test method.

As implied above, the finding of no agglutination in a cross-match done by the standard method using saline cell suspensions does not guarantee that there are no agglutinins present in the serum, or that the transfusion may not result in serious or even fatal hemolytic reaction. It is gradually becoming accepted practice in blood banks to do the cross-match testing by one or more of the newer methods. It is clear that the painstaking and time-consuming methods that may be necessary for the solving of difficult problems cannot be used for routine cross-matchings in the blood bank. The methods that will be outlined below represent the combined experience of several large blood banks and assure, within the limits of economic feasibility, the compatibility of donor and recipient.

"Serum Method" of Cross-Matching

A very satisfactory cross-matching technic involves the direct mixture of recipient's serum and donor's cells and vice versa and immediate centrifugation in small test tubes. Tubes of *clotted* blood from donor and recipient are centrifuged, if necessary, to separate cells and serum. Two drops of the recipient's serum are placed in one test tube (10 mm. x 70 mm. is a convenient size) and two drops of the donor's serum in a second. With a pair of round wooden applicator sticks (approximately 2 x 150 mm.) a few cells are removed from the donor's clot and mixed into the two drops of the recipient's serum in the first tube. The optimum number of cells thus transferred must be determined by experience, but in general a number sufficient to give a cell button about 5 mm. in diameter in the bottom of the tube after spinning makes for easier and more reliable reading of results. There is, however, an apparently wide margin of safety as far as the number of red cells is concerned. The recipient's red cells are similarly mixed with the serum of the donor in tube No. 2. Both tubes are immediately centrifuged with sufficient force to result in a well formed cell button and clear supernatant. Too vigorous centrifugation results in a cell button tightly adherent to and difficult to separate from the bottom of the tube, which makes estimation of the degree of true agglutination quite inaccurate. The tubes are examined immediately after centrifugation. The absence of agglutination in both tubes indicates almost surely that there is no incompatibility that could result in a hemolytic blood-transfusion reaction. This method has not failed to demonstrate high-titered "albumin-active" anti-Rh in a serum regardless of the possible presence

of prozone, when ordinary Rh-positive bloods were used. There is no guarantee, however, that all D^u variants would be agglutinated by this technic. Tubes showing no agglutination should be incubated at 37°C. for 20 minutes, respun and re-examined for agglutination. *It must be re-emphasized that immediate centrifugation is essential in this technic.* Anti-Fy^a and anti-Jk^a, if present in the recipient's serum, will not be demonstrated by this method, even when the donor is incompatible, but the method is still a good one and is preferable to the saline cross-match.

Kellner[4] has made extensive use of an additional technic that is as rapid and easy as the method outlined above and provides a valuable additional safeguard. He utilizes the trypsinization technic proposed by Wheeler and a specially selected test blood, according to the following method: A 4 per cent suspension of red cells from a Group O, Rh-positive (Rh_1Rh_2) donor (the same person every day) is made up in a 0.1 per cent solution, in saline, of crude Difco trypsin (1:250) and incubated at 37°C. for 10 minutes, after which the mixture is spun down, the trypsin solution is decanted and the cells are brought back to a 4 per cent suspension by the addition of fresh physiologic saline. A sufficient amount of trypsinized red-cell suspension is prepared for a day's use and a fresh preparation is made each morning, although the cells are probably satisfactory for use for forty-eight hours. It has been found that these trypsinized cells perform more satisfactorily if allowed to stand for two hours after their preparation before use, with fewer "false positive" reactions. When a cross-match test is set up a third tube is used, containing two drops of the trypsinized cell suspension and two drops of the recipient's serum. This third tube is spun down immediately, along with the other two, and examined for agglutination immediately after centrifugation. If agglutination is absent in all three tubes, the cross-match is reported as compatible with no further testing. Agglutination of the trypsinized red cells is presumptive evidence that the recipient's serum contains anti-Rh or some other abnormal blood-group isoantibody. This indicates that the recipient is a high-risk patient, as far as hemolytic transfusion reactions are concerned, and that further precautions are advisable. Accordingly, the first tube (the major cross-match) is incubated at 37°C. for thirty minutes, and the indirect Coombs test is performed on it. In performing the Coombs test, the technician should follow in detail the technic outlined in the package circular of the manufacturer.

In performance of the cross-match test as outlined above, a small percentage of cases will show apparent or real agglutination of red cells in one or more of the three tubes, which disappears when the Coombs test is applied. Most of these will be "false positives," which is a matter of no concern, other than that it may occur. It is not common, and the small percentage of such cases does not detract from the value of the method as a whole.

It should be pointed out that although the trypsinization of red cells makes them readily agglutinable in saline solution by anti-D and other antibodies of the Rh group, it does not enhance their ability to be agglutinated by serums containing anti-K or anti-Fy^a. The Coombs method is still the only method that can be relied on in regard to these antibodies.

Special Problems in Cross-Matching

Some of the special problems of cross-matching require comment. The patient with acquired hemolytic anemia may have circulating antibodies that agglutinate all blood cells, particularly when the more sensitive methods are used. These patients present difficult problems in the matter of selection of blood donors. It should be clearly understood that such patients, if they have had previous transfusions, frequently have *specific* blood-group antibodies in addition to the nonspecific panagglutinin characteristic of acquired hemolytic anemia. It is essential, therefore, to cross-match a number of potential donors and to use as donors those whose cells are least agglutinated by the recipient's antibodies, such selection necessarily involving the performance of multiple titer tests of patient's serum against donor bloods. The cells of these patients, of course, always give a positive direct Coombs test and will therefore necessarily give a "false" positive *indirect* Coombs test with any donor serum.

Troublesome agglutination of potential donor cells will also occur whenever the patient's or donor's serum has a nonspecific "cold" agglutinin of sufficient potency. In such cases warming of the tubes to 37°C. is sufficient to make the agglutination disappear. The nature of the agglutinin can be further investigated by reincubating at 4°C. and by showing that the serum agglutinates all bloods, including the person's own, at 4° C. Specific cold agglutinins, such as anti-P, rarely cause difficulty in the cross-match, and would be suggested by the finding that the person's own cells are not agglutinated by his serum.

Bacterial contamination may result in "false positive" agglutination. This will not be a troublesome factor when fresh serum and clean test tubes are used, but may be so when serums, especially donor serums, are kept for any length of time. It is important, therefore, to have some sterile serum from the donor available, either by making sterile transfers initially when processing the pilot tube or by having an extra, unopened pilot tube for checking purposes. In any event, it is worth while to take reasonable care to prevent gross contamination of the donor serums. Bacterial growth may also affect red cells so that they are agglutinated in any serum.

Rouleaux formation may occasionally be troublesome in cross-matching tests. Rouleaux are quite characteristic in appearance, however, and usually are of no significance. The serums of certain patients, especially those with myeloma, are particularly troublesome as far as rouleaux formation is concerned. It is recommended that cross-match tests that show rouleaux be checked by the Coombs method.

From time to time difficult problems will arise in any blood bank and will require the facilities of a specialized laboratory. It is well worth while to use such facilities when problems arise, even though it represents an additional cost to the blood bank. It is to be expected that new technics will be developed for blood-grouping tests, and that with new and better technics more and more of the problem cases can be handled by the individual blood banks.

TABLE 6. *Isoantibodies That Have Been Encountered in Human Serums.*

ANTIGENS	SALINE-ACTIVE ANTIBODIES	ALBUMIN-ACTIVE (OR SERUM-ACTIVE) ANTIBODIES*	ANTIBODIES DEMONSTRABLE ONLY BY COOMBS METHOD
A, B	Universal	+†	−
O	+	−	−
D, C	+	+	+
c, E, e	+	+	−
M, N	+	−	−
S, s	+	−	+
P	+	−	−
Lewis	+	−	−
Kell	+	+	+
Lutheran	+	−	−
Duffy	−	−	+
Kidd	+	−	+

*Inactive in saline.

†A plus mark in any particular column indicates that antibodies of that type may be encountered. Note the considerable number that may require the Coombs method for their detection.

Table 6 presents, in condensed form, the types of isoantibodies that may be found in human serums. It is well to note that there are several antibodies that may require the Coombs method for their demonstration.

UNIVERSAL DONORS

Universal donors have been used so extensively in the past that the use of Group O blood for general transfusion purposes has become a procedure of established merit. Certain types of hospitals, which use transfusion therapy almost exclusively on an emergency basis, have found that a blood bank stocked only with Group O blood meets their needs better than any other arrangement. There are two special hazards, however, in using Group O blood exclusively. One is the danger of mistyping A_3 donors as Group O. This danger can be virtually eliminated by doing back-typings. The second potential hazard is the so-called "dangerous universal donor" — the Group O person whose serum contains unusually high titers of anti-A or anti-B or both. Such persons should not be used as universal donors, since if their blood is given to a patient of Group A, Group B or Group AB, massive though sometimes slow hemolysis of the patient's cells may occur. Direct fatality from such hemolysis is rare, but further transfusions are usually made necessary, and it is a generally undesirable situation. At present there is no completely satisfactory method for screening out the dangerous "universal" donors. Until satisfactory methods can be worked out, the following procedure is recommended by Grove-Rasmussen[5]: To 0.1 cc. of the donor's serum add 0.2 cc. of the dilute solution of A and B substances (Sharp and Dohme) and let stand at room temperature for one hour. Add 2 drops of this mixture to each of 2 small test tubes. To one of these tubes add 2 drops of a saline suspension of Group A_1 red cells, and to the second a similar preparation of Group B red cells. Mix by gentle shaking and incubate for one hour at 37°C. The Coombs test is then applied to both these tubes. Group O donors whose serum fails to agglutinate both the A_1 and the B red cells by this method are considered to be "safe O donors." Approximately 50 per cent will be considered safe by this method.

The addition of 10 cc. of the 0.1 per cent solution of A and B substances to each pint of Group O donor blood is recommended whenever such blood is to be used for any recipient other than one of Group O or whenever the blood is to be set aside for emergency use.

DONOR SELECTION IN EMERGENCIES

It is customary in many hospitals to keep a pint of blood ready at all times for possible use in an emergency so acute that there is not time for preliminary tests of any kind before the transfusion is started. Such blood should be from a Group O, Rh-negative donor, whose serum has been shown to contain no anti-Rh antibodies or dangerous amounts of anti-A or anti-B.

Anti-Rh antibodies can be detected by testing the serum against the standard trypsinized blood recommended above as part of the cross-match procedure, or they can be identified by the Diamond–Abelson slide test method.[6] The slide test method utilizes oxalated blood, preferably one to three days old, from a Group O, Rh-positive (preferably O, Rh_1Rh_1) donor, plain glass slides and a warmed viewing box. A drop of the donor's serum and a drop of the test blood are mixed on a glass slide in an area approximately ¾ inch square, with square edges, and without the use of a wax circle. After the slide is placed on the viewing box, the box is tilted back and forth about twice a minute, and observed over a period of three to five minutes. Agglutination of the red cells by either method indicates the probable presence of anti-Rh antibodies in the donor's serum, and his blood would be a dangerous one for Rh-positive recipients.

Hazards of Isoimmunization in Blood-Transfusion Therapy

In addition to the risk of hemolytic transfusion reaction, which has already been described, and of pyrogenic and allergic reactions and of transmission of disease, which will be discussed in the following sections, the physician who gives a blood transfusion should be aware of the potential risk of immunizing a recipient to one or more of the blood-group antigens not tested for in the routine preparation for transfusion. At least a dozen of the blood-group antigens, besides A, B and D, are sufficiently antigenic to sensitize some of the recipients who lack them, with the likelihood, if sensitization occurs, of hemolytic reactions to future transfusions. Women so sensitized may have erythroblastotic babies in subsequent pregnancies. Such a risk should not deter one from giving needed blood transfusions but is one of the factors that make the giving of unnecessary (so-called "cosmetic") transfusions reprehensible. If the donor and recipient are properly matched with respect to A, B and D, the chances are still at least 80 per cent that the donor's cells have one or more antigenic blood-group substances that are lacking in the recipient's cells. The chances are somewhat less if donor and recipient are Rh-negative and somewhat greater if both are Rh-positive. Cross-match tests do not demonstrate this type of incompatibility. Fortunately, the likelihood of *actual sensitization* is small because of the low antigenicity of many of the blood-group substances. However, the risk is increased if the donor is the husband of the recipient, because of the possibility of previous sensitization by pregnancy and the possibility of erythroblastosis fetalis in subsequent pregnancies if sensitization occurs as a result of the transfusion. Husbands (or their immediate relatives) should not be used as donors for their wives if other donors are available. One fact must always be kept in mind when blood transfusions are given: Whether or not the result has any serious clinical significance, the possibility that any injected blood may sensitize the recipient to one or more blood-group antigens must never be overlooked and should be weighed against the actual need for transfusion. Certain patients are possibly greater risks in this respect, particularly those with lupus erythematosus, rheumatic fever or other "collagen diseases."[7]

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37361

PRESENTATION OF CASE

First admission. A twenty-four-year-old woman was admitted to the hospital because of fatigue and swelling of the legs.

The patient had never been ill until two and a half years before admission, at which time she suffered a severe generalized sunburn and was unable to walk for two weeks. One and a half years later she developed swelling of the right leg, which at first was red and warm. The redness disappeared, but the swelling subsided on bed rest. As the right leg began to improve the left leg began to swell in the same fashion. During the ensuing year one or both of the legs were swollen most of the time, but gradually this became less severe and at the time of admission only the ankles would swell on long standing. Examination at another clinic one year prior to entry revealed no abnormalities. During this period the patient lost at least ten pounds in weight, her appetite became poor and she "felt tired all of the time." Three months before admission she was told that she was anemic and iron was prescribed. Two weeks before admission she developed headache, vomiting, a temperature of 102°F., a dry cough and hoarseness. She was given aureomycin for three days, after which the temperature returned to normal. At this time it was noted that the hemoglobin was 50 per cent. During the week prior to admission she noted night sweating. She denied any previous fevers, bleeding tendencies, dysphagia, dyspnea, chest pain or joint symptoms.

Physical examination revealed a thin, apprehensive, chronically ill-looking woman. The voice was hoarse. The skin was pale, hot and smooth and the palms moist and cool. There were three patches of cotton-wool-like exudate in the fundi. The larynx showed no growth or paralysis of the vocal cords. The heart sounds were low-pitched and there was a Grade II to III apical systolic murmur, with an accentuated mitral second sound, that was audible at the base and along the left sternal border. A scratchy rub was heard transiently in the pulmonary area. The pulmonic second sound was greater than the aortic. The lungs were clear to percussion and auscultation. The spleen and liver were not palpable.

The temperature was 101.6°F. and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

Examination of the urine showed a + test for albumin and a specific gravity of 1.008; urobilinogen was positive in a dilution of 1:40. Examination of the blood disclosed a hemoglobin of 6.6 gm. and a red-cell count of 2,720,000. The red cells were markedly achromic and showed considerable variation in size and shape, with frequent elongated, tailed and oval forms and occasional stippled and target cells. There was a marked increase in the number of platelets. The reticulocyte count was 0.8 per cent and 3.3 per cent. The first blood Hinton test was positive and the second negative. The white-cell count was 4400, with 87 per cent neutrophils, 7 per cent small lymphocytes, 5 per cent monocytes and 1 per cent young lymphocytes. A smear of bone-marrow aspirations showed 5 per cent erythroid cells, 90 per cent myeloid cells and 5 per cent lymphoid cells. The myeloid-erythroid ratio was 18:1. The myeloid maturation was orderly and the megakaryocytes were normal. No tumor cells were recognized. The nonprotein nitrogen was 19 mg., the alkaline phosphatase 4.8 units and the total protein 7.42 gm. per 100 cc., with an albumin-globulin ratio of 1. The bromsulfalein retention was 24 per cent in 2 hours, the cephalin flocculation +++ in 24 and 48 hours and the prothrombin time 20 seconds (normal, 19 seconds). Of three blood cultures, one grew *Staphylococcus albus* and *Staphylococcus aureus*. The stool cultures were negative for pathogens. The Widal and brucella agglutination tests were negative. Seven stool examinations were guaiac negative. A needle biopsy of the liver showed acute congestion.

An x-ray film of the chest showed several calcified scars in the right lower lung regions but was otherwise normal. The heart was at the upper limit of normal in size. The spleen was questionably enlarged. A gastrointestinal series and barium-enema examination were negative. The temperature ranged between 100 and 103°F. daily, being highest in the afternoon, but the patient did not feel "feverish." She was given two whole-blood transfusions and Chloromycetin. The hemoglobin rose to 11.2 gm., and the patient was discharged on the seventeenth hospital day showing no essential improvement.

Second admission (ten weeks later). The patient remained at home in the interval, during which time she received three transfusions at a

local hospital and took liver, vitamin B_{12} and iron. After a course of terramycin the temperature fell to 99 to 100°F. for a short period. She continued to have cough and developed abdominal pain and nausea. Another x-ray examination of the chest and a bone-marrow aspiration, performed elsewhere, were said to be negative. An intravenous pyelogram was also negative. The patient entered this hospital for further diagnostic study.

Physical examination revealed a few small cervical and axillary lymph nodes. The tip of the spleen was palpable. The right upper quadrant felt doughy, but no definite mass could be made out.

The urine had a specific gravity of 1.014 and gave a ++ test for albumin; the sediment contained frequent granular casts and uric-acid crystals. Examination of the blood revealed a hemoglobin of 3.8 gm., a red-cell count of 1,370,000, with 3.8 per cent reticulocytes, and a white-cell count of 10,200, with 94 per cent neutrophils. An x-ray examination of the chest and abdomen demonstrated no new findings.

The temperature showed a diurnal variation to 102 or 103°F. The patient received three whole-blood transfusions of 500 cc. each and three transfusions of packed red cells. A transient nonbloody diarrhea was controlled with paregoric. She was given 4 mg. of nitrogen mustard intravenously daily for three days without effect on the fever and was discharged on the seventh hospital day, with a hemoglobin of 12 gm.

While at home she developed severe jaundice and abdominal distention, slowly lapsed into coma and died eight days after discharge.

Differential Diagnosis

Dr. Walter Bauer*: Before discussing this case I should like to ask a few questions. Can anyone tell me anything more about the appearance of the legs? Was the skin warm and adherent to the underlying tissue? What was the nature of the swelling? Was there evidence of venous obstruction?

Dr. Alfred Kranes: It was very difficult to get a history from the patient. All she told us was that at the beginning the legs were swollen, warm and quite red, with superimposed red spots, but not painful. Whether or not the edema was pitting I do not know.

Dr. Bauer: Additional information concerning these points might be helpful in establishing the diagnosis. Edema of first one leg and then the other suggests the possibility of thrombophlebitis migrans; however, this would be unusual in a twenty-four-year-old woman who was otherwise well. The onset as recorded is rather like that of dermatomyositis, although the subsequent course was not.

*Chief, Medical Services, Massachusetts General Hospital.

Was there any evidence of collateral circulation at the time the legs were swollen? Was there evidence of venous stasis?

Dr. Kranes: The information was very meager.

Dr. Bauer: I assume the patient was not jaundiced at the time of the first admission?

Dr. Kranes: She was jaundiced only terminally.

Dr. Bauer: Can we be certain that a "cotton-wool-like exudate" was present in the fundi? That is important from my point of view. Was it like the exudate seen in lupus erythematosus?

Dr. Kranes: I can describe them for you, Dr. Bauer; what they represented is a matter of interpretation. There were three white fluffy-looking spots near the disk.

Dr. Bauer: Was the Grade II apical systolic murmur heard several times or just once?

Dr. Kranes: It was heard several times, but it did come and go.

Dr. Bauer: Possibly the systolic murmur heard along the left sternal border may have been aortic rather than mitral in origin. Have you any idea how long she received Chloromycetin and terramycin?

Dr. Kranes: Over a period of five weeks, in inadequate amounts. She was a very difficult patient and would not swallow pills. She insisted she could only take liquid medicine.

Dr. Bauer: I take it the nitrogen mustard affected nothing but the fever?

Dr. Kranes: There was no appreciable effect while she was in the hospital. Whether the subsequent course was due to that I do not know.

Dr. Bauer: Nitrogen mustard is employed for many diseases nowadays, including Bright's disease, rheumatic fever and rheumatoid arthritis. Maybe it was not given for the treatment of lymphoma.

Were the x-ray films helpful?

Dr. Stanley M. Wyman: Not particularly.

Dr. Kranes: They were reported to be negative.

Dr. Bauer: Dr. Bernard M. Jacobson informed me that the bone-marrow aspiration revealed one abnormality — a marked increase in the myeloid-erythroid ratio, 18:1 instead of 36:1. This finding must be interpreted as red-cell arrest and myeloid activity. In cases of this type I always wonder whether a bone-marrow aspiration is as helpful a diagnostic procedure as a bone-marrow biopsy. In this case I assume it was. If she had invasion of the bone marrow by tumor cells, bone-marrow biopsy as well as aspiration may have missed the lesion. In cases in which the diagnosis is in great doubt it is better to do a bone-marrow biopsy than an aspiration.

I am dealing with a twenty-four-year-old woman whose first problem is that of an unrelentingly progressive anemia. Dr. Kranes had inferred that the nitrogen mustard may have had something to do with the death. I had not entertained that pos-

sibility. This patient had an illness that began with swelling of the legs and later showed a "cotton-wool-like" exudate in the fundus and an anemia due to red-cell arrest, with or without a slight degree of hemolysis.

DR. KRANES: Would it help you to know that Dr. David Cogan called the eye-ground changes a "cotton-wool-like exudate"?

DR. BAUER: It would help, but I am still not too comfortable.

The patient finally developed an enlarged spleen, and she may or may not have had a few enlarged posterior-cervical and axillary lymph nodes. Whether the lymph nodes became palpable because of the loss of weight is not known.

I considered the possibility of some type of poisoning, — benzol. Personally, I doubt it. In the light of the patient's dying with severe jaundice, I wonder whether or not she may have had a low-grade viral hepatitis during the entire time. That does not explain some of the findings that have been reported. One could not help wondering about the possibility of a low-grade septicemia, particularly if it was staphylococcal, but again there are many things against this diagnosis. I cannot entertain that diagnosis seriously.

I wondered whether this patient had rheumatic heart disease with a superimposed subacute bacterial endocarditis; when caused by a staphylococcus the resulting illness can be long-drawn-out, lasting as long as eighteen months. There are many things against it. The anemia in this case was extremely severe. Despite good blood replacement the hemoglobin returned to 3 gm. and the red-cell count to 1,370,000 in a few weeks.

When first I read this case report I thought this might have been another case of what we term "group disease." We include under this term rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis and polyarteritis nodosa. I cannot believe Dr. Castleman would pick out another such case for me. A white-cell count of 4000, with 87 to 95 per cent neutrophils, is most unusual in lupus erythematosus. During the terminal pneumonitis of lupus erythematosus the rise in neutrophils is a manifestation of a leukocytosis. As stated previously, I also entertained the possibility of dermatomyositis because of the type of onset. Against this diagnosis is absence of muscle pain and residual evidence in the lower extremities, which would be most unusual. One might also expect some calcification in the adipose tissue of the legs. The ocular findings and mild, increasing renal involvement are further reasons for considering the possibility of one of the group diseases. I must say that I think I am on very thin ice in entertaining such diagnoses, and for that reason I hoped Dr. Kranes would say the "cotton-wool exudate" could have been tumor or tubercle.

I can frankly say, as many have said in this pit before, that I do not know the cause of this patient's death. I shall guess lymphoma, probably of the Hodgkin type. Against this diagnosis are the many negative observations recorded in the clinical record, including two bone-marrow aspirations. If my guess is wrong I can fall back on the failure to obtain a biopsy! I appreciate that some things are left unexplained by lymphoma, particularly the exudative lesion in the fundus. I shall be glad to stand questioning.

DR. BERNARD M. JACOBSON: I should like to say that that type of exudate can be seen in any anemia and is usually due to edema.

DR. BAUER: Can it disappear without any scar?

DR. JACOBSON: We see them frequently in pernicious anemia, — they disappear in a week. As far as the blood picture is concerned, I think it is that which is present in lymphoma. I agree that the bone-marrow aspiration does not rule out lymphoma. Certainly a bone-marrow biopsy should be taken when one suspects lymphoma, granuloma or carcinoma.

DR. EDWARD D. CHURCHILL: Why do you put off the positive staphylococcus blood picture?

DR. BAUER: Dr. George Holmes taught us that patients with staphylococcus septicemia of this duration were very likely to have bilateral lung abscesses and abscesses of the cortex of the kidneys. Next to lymphoma, some type of subacute bacterial endocarditis would appear to me to be the most likely diagnosis. However, it is unusual not to have more evidence of bacteremia and other signs of subacute bacterial endocarditis after eighteen months.

DR. KRANES: After the blood was brought up to normal level by transfusions the murmur was nearly gone.

CLINICAL DIAGNOSIS

Fever of unknown origin.

DR. BAUER'S DIAGNOSIS

Hodgkin's lymphoma.

ANATOMICAL DIAGNOSES

Miliary tuberculosis.
Tuberculous peritonitis.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: As I read this history, it reminded my very much of the cases that Dr. Cabot used to discuss over twenty-five years ago. In those days there were very few complicating laboratory tests other than red-cell and white-cell counts and an occasional urine examination. I think he probably would have taken this case up from the

point of view of prolonged fever, which he used to define as a fever lasting more than six weeks. In such cases he always went through a list of three diseases, — typhoid fever, tuberculosis and sepsis. Sepsis included endocarditis, of course, with streptococcus or staphylococcus as possible agents.

At post-mortem examination the pathologist was faced with a difficulty. We were given permission to make a five-inch incision, and we had to decide where that incision should be made. It was eventually made in the lower abdomen, and a severe fibrinous peritonitis was found. As the fibrinous exudate was stripped away from the peritoneal surfaces many little pearly foci became obvious. Further exploration showed that both tubes were markedly enlarged, inflamed and full of caseous exudate. We were only able to obtain "biopsies" of the liver, spleen and the lower lobe of the lung. Bone marrow was obtained from one of the vertebras. Sections showed a very characteristic tuberculous process in all areas. The tuberculous salpingitis was probably the focus of infection from which a diffuse but dry type of tuberculous peritonitis developed. The retroperitoneal lymph nodes were also involved. It is not impossible that a bone-marrow biopsy might have shown a miliary tubercle. We had a chance to find one also in the ante-mortem liver biopsy, but none were present. I cannot tell you anything about the condition in the legs, and we have not the clear explanation of the jaundice that I should like. The extrahepatic bile ducts were patent to probe. There was one rather large caseous lymph node in the juncture of the hepatic and common duct, which may have caused obstruction of the common duct from external pressure; we could not be certain.

DR. BAUER: I was wondering about the exudate in the eyes. Is it not one of the features of tuberculosis?

DR. KRANES: I specifically asked Dr. Cogan about that, — whether they could be miliary tubercles. He said he did not think so.

CASE 37362

PRESENTATION OF CASE

A seventeen-year-old boy was admitted to the hospital because of pain in the left leg.

Three days prior to admission while water skiing the patient lost his right ski; this caused him to somersault. He experienced considerable pain in the left thigh after this but was able to keep afloat. For the next two days he could walk, but the pain became progressively more severe, forcing him to seek medical attention.

He had had no serious illnesses or accidents in the past. A short time before the accident he had a "boil" in the right ear that was treated with penicillin.

Physical examination revealed a well developed youth. The heart, chest and abdomen were normal. Flexion, internal rotation and abduction of the left hip were limited by pain, which radiated into the inguinal and gluteal regions. No definite area of tenderness was found on external palpation, but on rectal examination a mass was palpable as a slightly tender bulge on the left side of the rectum.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood revealed a hemoglobin of 16.0 gm. and a white-cell count of 7400. A urinalysis was negative. X-ray films of the pelvis showed a cystic area measuring about 7.0 cm. in length and 4.5 cm. in width, lying in the left ischium and extending to the lower aspect of the acetabulum. The bone here was expanded and greatly thinned, and a jagged fracture extended from the superior aspect of the cyst down through the cyst and also to its lateral aspect. There was some mottled calcification in the soft tissues close to the bone. The lesion was characterized by expansion and thinning of the bone, a lack of trabeculae and no appreciable destruction of neighboring bone or significant periosteal new-bone formation. There was no evidence of a soft-tissue mass about the lesion (Fig. 1). The remainder of the pelvis, the upper femurs and the lumbar and sacral spine were normal.

FIGURE 1.

On the sixth hospital day an operation was performed.

Differential Diagnosis

Dr. James J. McCort*: One might begin this discussion with an enumeration of the significant facts available from the protocol. The patient is a seventeen-year-old boy with a bone-replacing and expansile lesion in the left ischium that was completely asymptomatic until a pathologic fracture was sustained. The temperature, pulse and respiration were entirely normal, as were the blood count and urinalysis. The physical examination was entirely negative except for the rectal tenderness.

As the first step in the differential diagnosis, an infectious process can be excluded. A pyogenic infection or tuberculosis of bone would be expected to cause pain and produce systemic symptoms early in the course of the disease. Furthermore, the x-ray appearance of this lesion differs from that caused by infectious agents, in that the latter are never strictly expansile.

It is also possible to remove from consideration the possibility of malignant tumors, either primary or metastatic. Malignant bone tumors are characterized by irregular bone destruction, periosteal new-bone formation and development of a soft-tissue mass. None of these features are present in the case under discussion.

From the evidence at hand, there is nothing to favor the diagnosis of metabolic bone disease. The bone adjacent to the lesion was entirely normal. No other lesions were apparent in that portion of the skeleton included in the initial examination. No calculi were seen in the course of either urinary tract to suggest hyperparathyroidism.

Other benign conditions whose exact etiology is disputed, such as eosinophilic granuloma and osteoid osteoma, do not, to my knowledge, cause this degree of expansion of the cortex, and they tend to show a well defined margin.

By a rapid process of exclusion, it is possible to say that the lesion under discussion must have been nonmalignant, noninfectious and nonmetabolic. Unfortunately, a large number of possibilities still exist.

Since the study of Von Ebner† in 1875, it has been known that normal bone is in a constant state of change; while one portion is undergoing absorption in which the osteoclasts take part, other portions are undergoing reconstruction by osteoblasts. This simultaneous process of erosion and regeneration takes place throughout life and is most vigorous during skeletal maturation. It is likewise during this period of rapid growth leading up to skeletal maturity that derangements of the orderly process of bone formation and bone destruction are likely to occur. Thus, under twenty years of age, an arrest or error in normal bone development such as fibrous dysplasia, giant-cell tumor, benign bone cyst, chondroma, myxochondroma, fibroma, neurofibroma, hemangioma or lymphangioma may develop. Depending on the size and strategic location of these so-called benign bone tumors or tumors associated with trauma, as in the case at hand, symptoms may develop to arouse the patient's attention. Undoubtedly in many cases the lesion, if small and not subject to trauma, may persist for many years undiscovered.

In this patient, the bone lesion is composed of soft tissue that in its growth had expanded the shaft. The overlying cortex is thinned but not broken except at the site of the pathologic fracture. As stated in the protocol, there is no periosteal new-bone formation, no spicule formation and no apparent soft-tissue mass. A few coarse and poorly defined trabeculae pass through the lesion, and it has a somewhat ground-glass appearance, as if not all the bone within it had been eroded. Furthermore, the margins of the lesion are not clear-cut. In the protocol the lesion was called a "cyst." A "soft-tissue tumor" would be a better term, as from the x-ray appearance alone it is not possible to demonstrate the presence of fluid.

In developing the differential diagnosis, the possibility of myxochondroma, neurofibroma, fibroma, hemangioma or lymphangioma of bone would seem to be less likely, as these tumors do not produce exactly the type of x-ray picture seen here. In them the persistent trabeculae are most dense and irregular. A zone of sclerotic bone frequently surrounds them. In addition, they are statistically rare. Nevetheless, the possibility of one or the other cannot be entirely excluded.

Among the remaining possibilities, — fibrous dysplasia, giant-cell tumor and bone cyst, — further exclusion is extremely difficult. Because the patient was under twenty, because of the presence of expansion of the cortex without destruction except in the area of fracture and because of the ill-

*Associate radiologist, Massachusetts General Hospital.

†Von Ebner, V. Über den feineren Bau der Knochensubstanz. *Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl.* 72:49-138, 1875.

defined coarse trabecular pattern with the absence of a clear-cut border, I favor a diagnosis of fibrous dysplasia. It is well known that these lesions may exist in the absence of other extraskeletal manifestations. There was, as mentioned, a pathologic fracture.

DR. PAUL ZAMECNIK: Would a giant-cell tumor do that?

DR. MCCORT: Yes, it would. As I said during my discussion, I cannot rule out a giant-cell tumor or a bone cyst. Fibrous dysplasia seems to me to be the most likely of the three possibilities.

CLINICAL DIAGNOSIS

Tumor of ischium.

DR. MCCORT'S DIAGNOSIS

Fibrous dysplasia of ischium.

ANATOMICAL DIAGNOSIS

Unicameral bone cyst of ischium.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient, as Dr. McCort prophesied, was operated on for purposes of exploration and biopsy. When the lesion was exposed a needle was inserted into it and fluid was readily withdrawn. Subsequently a window was made in the cortex that opened down onto a well defined cystic cavity and the entire area of involvement was resected. The microscopical picture of a simple bone cyst is not particularly characteristic; it is much more easily recognized from the gross appearance than from the microscopical slide. The most important function of the microscopical examination is to rule out other possibilities, such as neoplastic tissue or the presence of a chitinous membrane, which would be found if the cyst represented hydatid disease. Nothing of that sort was found, and our diagnosis was unicameral bone cyst.

DR. MCCORT: Were trabeculae present within the cyst, or was it a solitary cavity?

DR. MALLORY: Trabeculae were not noted, and it was definitely a single cavity.

Inasmuch as this boy had spent his entire life in New England, the possibility of parasitic disease was not very seriously considered. In some parts of the world that would rank high among the possibilities with such a lesion. Would the x-ray appearance differ significantly, Dr. McCort?

DR. MCCORT: The x-ray appearance is said to be quite similar.

DR. BENJAMIN CASTLEMAN: I believe this is the first case of unicameral bone cyst that we have seen in the ischium. If this x-ray shadow were seen in the upper humerus where most of the bone cysts occur, I am sure bone cyst would have headed the list of diagnoses.

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STRIP-TEASE THERAPEUSIS

THE cancer cures that are announced "in the vestments of scientific orthodoxy"* and fail to live up to the publicity that is accorded them may cause as many heartaches as the out-and-out frauds that are perpetrated on the public. During the past ten years such new cancer cures have been altogether too frequently announced to the reporters and the patients. The technic is always the same; it has for many years been successfully used in burlesque shows to reach the public and make it pay through the nose. In medicine the motive is less tawdry, often being a mixture of egoism and enthusiasm in some scientifically myopic person.

The promised beauty is advertised glamorously, with pleasingly rounded contours demurely draped in classical garments. The show opens with the exciting announcement that twin tumors have been caused to disappear and that if the audience will wait patiently — not too much handclapping, please — something better is just around the corner. Glover's serum, Coffey–Humber serum, ensol, antireticulocytotoxic serum from the steppes of Russia — all have had their applause and retired. Today the newest top-billing peroxide ingénue is to perform. After the heavy velvet has been shed, the filmy scanties are revealed — but not completely. The new wonder doesn't exactly cure; it almost cures. The show proceeds with restraint, — decorous restraint eliciting a little less handclapping and a little more publicity and support. As each of the seven veils is shed the promise is greater, but there is always a catch. The spectators and "the patients have less pain. Finally they just fade away." Even the metaphors become confused — but the performance in the last analysis is just plain shoddy — a sophisticated version of Mark Twain's Royal Nonesuch.

Nor is cancer the only fertile field for both authentic and profound, as well as fanciful and frothy, research. In schizophrenia, mongolism and multiple sclerosis, to name but three conditions, strip-tease therapeusis has occasionally been paraded before the public, in the form of endocrine and/or glutamic-acid cures, — well, not exactly cures but "improved performances," revealed "in the vestments of scientific orthodoxy."

For the ethical and proper announcing of advances in medicine, physicians are honor bound to present their findings before scientific and medical forums, to submit their manuscripts to appropriate journals and to abide by the judgment of their peers, — which is necessarily and rightfully conservative on the matter of accepting widely-touted discoveries at face value on one person's say-so. No significant contribution can be withheld through reactionary opposition. The mission of the investigator is to present new facts, open to scientific analysis, duplication and verification by others. It has been found tedious and unfruitful to have to confirm work performed with secret formulas and recipes — even if trademarked. In a scientific paper, a fully-revealed factual content is the only

*Cameron, C. S. "They just fade away." *Ca: Bulletin of Cancer Progress* 1: May, 1951.

basis for its conclusions, and it is of critical importance that therapeutic studies be adequately controlled.

For the proper evaluation and understanding of research directed toward "curing" hitherto incurable diseases, the applauding public is respectfully urged to read not only the newspapers, *Arrowsmith*, *The Citadel* and *Men in White*, but the lowly *Adventures of Huckleberry Finn*.

"I've done considerable in the doctoring way in my time," says the Duke of Bilgewater. "Layin' on o' hands is my best holt — for cancer and paralysis — and sich things; and I can tell a fortune pretty good when I've got somebody along to find out the facts for me."

THE G. P.'S HOSPITAL

ESTABLISHED in 1862, when the clouds of civil war hung most heavily over the northern states of the union, the New England Hospital for Women and Children has for eighty-nine years been carrying on its own program of emancipation. A courageous exponent of woman's place in medicine, this respected institution has not only provided a constant training ground for the woman physician: it early established the country's first authentic school for nurses and produced as its first graduate Linda Richards, who was called shortly thereafter to found the training school at the Massachusetts General Hospital.

During these nearly fourscore years the New England Hospital has been an organization of women, conducted for and by women; it has been administered by women and staffed by women, and its patients have been women and their children. When the men of the profession have been admitted within its cloistering walls it has been only for consultation, and by courtesy.

The war between men and women seems to be languishing, however, perhaps for lack of animus. Women are accepted nowadays at even the Harvard Medical School, — if not as equals to men, at least as their superiors, — and the New England Hospital for Women and Children, also broadminded, is burying its own hatchet. A year ago it emerged from its self-imposed purdah, admitted men to its wards (certain selected ones), accepted them on its staff, engaged the first trousered administrator in its history, dropped the women and children from its title and became a general hospital.

This change is by no means a striking of its colors. The New England Hospital will not be a general hospital like any other, for it will still have its cause for which to fight and its crusade on which to march. This new championing will be that of the general practitioner, and with the recent decision of the trustees to establish a section of general practice, a determination has been shown to provide an antidote for the current poison of overspecialization.

The New England Hospital has no quarrel with specialists; it needs them and recognizes them as any hospital does. What it also recognizes is the fact that the family doctor needs in equal measure encouragement and the opportunity for doing good work and caring for his patients in a modern, well-equipped hospital.

The New England Hospital trustees envisage more than a staff section of general practice. They envisage also a training program and a residency in this most useful field of medicine. They wish to have their institution known as the hospital that trains family doctors.

NEW EDITOR OF CASE RECORDS

THE Case Records of the Massachusetts General Hospital, which first began independent publication under the editorship of Dr. Richard C. Cabot in 1911, have been a regular feature of the *Journal* for nearly twenty-eight years. This association, it may be stated with confidence, has been mutually advantageous, with the cases constituting one of the *Journal's* most popular features.

The excellence of these publications has obviously reflected the caliber and the interest of their editors and in this respect good fortune — as well as good judgment — has consistently attended them. Dr. Cabot continued as editor until his retirement in 1935, when he was succeeded by Dr. Tracy B. Mallory, pathologist-in-chief of the hospital. During Dr. Mallory's military service from 1943 to 1946 Dr. Benjamin Castleman became acting editor,

continuing as associate editor on Dr. Mallory's return.

The wheel has now completed another full cycle. Dr. Mallory, after giving of his time, his interest and his sagacity to the discussion and publication of the records for nearly fifteen years, has retired to the position of consulting editor, turning over the entire responsibility for this unique feature of the *Journal* to Dr. Castleman.

The Case Records will be in favored hands, tried and true; their continuance on the usual high plane is assured to their readers. It is nevertheless to be hoped that Dr. Mallory will be a consultant in fact as well as in name and that he will contribute to the discussions as often as he finds it convenient or can be persuaded to participate.

In this changing of the watch in the conduct of the "Cabot Case Records" one is again reminded of the terse statement that "what is excellent, as God lives, is permanent."

FAMILY DOCTOR

In line with the precedent established by the American Medical Association a few years ago, although not necessarily as a result of it, the British Medical Association has this year added to its list of periodicals a monthly magazine for the lay reader.

Family Doctor, the first issue of which appeared in April, follows its own pattern in serving the same functions that *Today's Health* fulfills in this country. It is not only a practical public-health publication that carries its message direct to the people: it is a public-relations instrument of almost incalculable value.

It is natural that in the midst of a world revolution all the old, accepted, conservative institutions should be on trial — medicine, one of the most conservative of all, among them. In this country medicine is today facing one of its greatest challenges of all time; circumstances have driven the profession in Britain much nearer to the point of no return.

One clearly logical line to follow in preserving or restoring the freedom and the dignity of medical practice is to demonstrate constantly to the public, — which in the long run decides these matters, — not only the indispensability of good medicine but its good will and its desire to serve unselfishly. Such publications as *Today's Health* and *Family Doctor* represent as good examples of this unselfish attitude as one might wish.

The British Medical Association is to be congratulated, in these anxious days for publishers of rising printing costs and paper shortages, on having embarked on this thoroughly benevolent enterprise.

The citizens of Auburn have secured the location of the proposed College for females, to that city, by subscribing $20,000 towards its establishment.

Boston M. & S. J., *September 10, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Dainty — George W. Dainty, M.D., of Monument Beach, died on March 24. He was in his sixty-seventh year.

Dr. Dainty received his degree from Tufts College Medical School in 1907. For many years he was chairman of the school committee in Bourne. He was on the consulting staff and a director of the Barnstable County Sanatorium in Bourne and on the consulting staffs of the Cape Cod Hospital in Hyannis and Tobey Hospital in Wareham. He was a fellow of the American Medical Association.

Newton — Ralph W. Newton, M.D., of Santa Rosa, California, died on July 21. He was in his seventy-seventh year.

Dr. Newton received his degree from New York University Medical College in 1898. He was a fellow of the American Medical Association.

His widow and two sons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TUBERCULIN, OLD, DILUTED

The Biologic Laboratories of the newly established Institute of Laboratories announce that beginning about September 1, Tuberculin, Old, Diluted will be available for distribution. This material has been prepared to fill a need for tuberculin that is ready for use in intracutaneous testing (Mantoux test).

Tuberculin, Old, Diluted is in one strength only; 0.1 cc. contains 0.1 mg. of O. T. international standard (sometimes expressed as 10 tuberculin units [TU]). The strength has been standardized to represent an "in-between" dilution. Old Tuberculin, distributed either commercially or from this

laboratory, has varied greatly in the past. Only in recent years have attempts been made at standardization.

It is believed that Tuberculin, Old, Diluted will reveal about 90 per cent of the positive subjects who would react to a 1-mg. dose (100 TU). The Tuberculin, Old (concentrated) will continue to be available to those who prefer to make their own dilutions or wish to retest any negatives with a stronger dilution. As now distributed, the concentrated tuberculin, when properly diluted as recommended, will contain .02 and 2.0 mg. per 0.1 cc. (2 TU and 200 TU).

JOHANNES IPSEN, M.D.
Superintendent
Institute of Laboratories
Boston 30

NONCLINICAL NOTES

Dr. Walter Bauer, formerly associate professor of medicine at Harvard Medical School and physician at the Massachusetts General Hospital, has been appointed Jackson Professor of Clinical Medicine at the medical school and chief of medical services at the hospital.

Dr. Clinton Van Zandt Hawn of Cooperstown, New York, has been appointed associate professor of pathology at Harvard Medical School and pathologist-in-chief of Peter Bent Brigham Hospital.

Dr. Geoffrey Edsall, head of the Department of Microbiology at Boston University School of Medicine, has been granted a one-year leave of absence to serve at Walter Reed Army Hospital, Washington, as head of the Immunologic Division and director of the Division of Biologic Products at the Army Medical Service Graduate School.

CORRESPONDENCE

EFFECT OF CORTISONE AND ACTH ON TUBERCULOUS INFECTION

To the Editor: The Committee on Therapy of the American Trudeau Society wishes to ask the co-operation of the medical profession in a survey of the possible deleterious effects of cortisone and ACTH on tuberculous infection in man. Experimental work has indicated this possibility, and scattered clinical experience has suggested that both compounds may have a harmful effect in human tuberculosis.

The American Trudeau Society, through its committee on therapy, is anxious to obtain information confirming or disproving this impression, and desires to ask the co-operation of physicians throughout the country in collecting pertinent data, as outlined below. Since tuberculosis is a common chronic disease, it seems likely that many physicians have had an opportunity to observe the effects of ACTH or cortisone on tuberculous infection coincident with the treatment of other disease states. The committee believes that this information is of sufficient importance to make such a study worth while, for if suitable material can be collected it would provide information of considerable significance that otherwise might not be available for years to come.

It is understood, of course, that the committee in no way wishes to interfere with the publication of results by individual workers contributing to this study and will respect any restrictions in the use of material.

Information is desired concerning both pulmonary and extrapulmonary tuberculosis, as to whether any clinician has observed any of the following: no apparent effect in patients with known active tuberculosis; an exacerbation of clinically active or apparently inactive tuberculosis during or after treatment with ACTH or cortisone; a favorable effect in active tuberculosis.

If such cases are available, the following data would be greatly appreciated: a brief clinical history, including a statement concerning the disease for which treatment was given, and whether or not active or inactive tuberculosis was suspected before treatment was begun; pertinent laboratory data, including results of sputum examination for tubercle bacilli; and the temporary loan of any available representative x-ray films related to the tuberculosis, before, during and after treatment. This information should be sent to Dr. Robert H. Ebert, University of Chicago Clinics, 950 East 59th Street, Chicago 37.

WILLIAM B. TUCKER, M.D.
Chairman, Committee on Therapy
American Trudeau Society
Minneapolis, Minnesota

BOOK REVIEWS

Regional Orthopedic Surgery. By Paul C. Colonna, M.D. 8", cloth, 706 pp., with 474 illustrations. Philadelphia: W. B. Saunders Company, 1950. $11.50.

This textbook of orthopedic surgery is dedicated to the late Dr. Royal Whitman. In the preface the author quotes from Nicholas André that orthopedics is the art of preventing and correcting deformities of the body in children and then traces the widening of its scope and its modern industrial and social implications. He begins with a most helpful discussion of the physiology of the muscular and skeletal systems. The book departs from the conventional manner of discussing diseases or related pathologic processes by considering each anatomic portion of the body in turn. It makes for easier teaching, particularly in discussing the examination of the various parts of the body, and it seems to be an effective manner of presenting the general principles of orthopedic surgery. The volume presents no new material but simply a new approach. It reflects the conservatism of the author. It is modern but reflects no fads. It is particularly adapted to the teaching of medical students, in that it teaches the principles of orthopedic care rather than special methods or technics. Usually only one form of treatment is suggested, but sufficient direction is given for the general care of each disability. This is a wise method of teaching, as the medical student or general physician has not had sufficient experience to choose from a large number of possible treatments.

The book is well written, and the illustrations are good. At the end of each chapter a short list of references is given. Although it may not be sufficiently voluminous or detailed for the orthopedic surgeon, it is the best book that has yet appeared for the teaching of orthopedic surgery to medical students and as a reference book for the general physician.

J. G. KUHNS, M.D.

New and Nonofficial Remedies. Issued under the direction and supervision of The Council on Pharmacy and Chemistry, American Medical Association. 782 pp. Philadelphia: J. B. Lippincott Company, 1951.

This up-to-date, practical pharmacopeia of Council-accepted products is indispensable to the staff of a medical journal as well as to pharmacists and, directly or indirectly, to the entire medical profession. The new edition has undergone more than the usual annual revision, with modification of the rules for admission of articles, the rewriting of some chapters and the addition of others.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. By Lawson Wilkins, M.D., associate professor of pediatrics, Johns Hopkins University School of Medicine, and physician, Harriet Lane Home and Johns

Hopkins Hospital, Baltimore. 4°, cloth, 384 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1950. $13.00.

This important new book in the special field of endocrinology in children and adolescents is an essential work for all pediatricians, endocrinologists and medical libraries. The preliminary chapters deal with the general topics of the endocrine relations to growth and development and the methods of endocrine study and diagnosis. These are followed by chapters on disorders of the thyroid gland, dwarfism, variations in the pattern of adolescent development, sexual precocity of "isosexual infantilism," four chapters on the adrenal cortex and its syndromes, heterosexual development, diabetes insipidus, pituitary tumors and intracranial lesions causing endocrine disorders, calcium and phosphorus metabolism – parathyroid disorders and tetany, carbohydrate metabolism and spontaneous hypoglycemia, obesity and congenital anomalies sometimes mistaken for endocrinopathies. Lists of important references are appended to the various chapters, and there is a good index.

Physicians' Federal Income Tax Guide and Simplified Accounting Record. 1951 edition. For the preparation of 1950 returns and 1951 estimates. By Hugh J. Campbell and James B. Liberman. 4°, paper, 125 pp. Great Neck, New York: Doniger and Raughley, Incorporated, 1950. (Also, Supplement No. 1, December 11, 1950.) $2.50.

This tax guide should prove invaluable to physicians in making out their income-tax reports. Supplements are issued from time to time whenever changes in the tax laws make them necessary.

An Index of Tumor Chemotherapy: A tabulated compilation of data from the literature on clinical and experimental investigations. By Helen M. Dyer, biochemist, National Cancer Institute, National Institutes of Health. March, 1949. Oblong 8°, paper, 329 pp. Bethesda, Maryland: Federal Security Agency, United States Public Health Service, 1950.

This index is arranged in tabular form and lists 5031 citations collected from the literature on the subject. The tables show the agent used, the type of tumor, the host and the therapy, including the effect claimed. Appended to the tables is a bibliography of 2213 references The book should be in all collections on tumors and on chemotherapy. It is an outstanding bibliography.

Surgery of the Eye: Injuries. By Alston Callahan, M.S. (Ophth.), M.D., professor of ophthalmology, Medical College of Alabama, and director, Thigpen-Cater Eye Hospital, Birmingham, Alabama. 4°, cloth, 217 pp., with 333 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $11.50.

This monograph is based on the experience gained by the author at an Army ophthalmic center in the study of 3000 men with injuries of the eye and adnexa. Since the war the author has had five years' further experience at the Thigpen-Cater Eye Hospital and has been able to follow many of the cases during a period of six or seven years. The text is divided into sixteen chapters, to which lists of selected references are appended. There are 21 color plates and many other fine illustrations. This is a de luxe publication at a reasonable price and should be in all collections on ophthalmology.

A Syllabus of Laboratory Examinations in Clinical Diagnosis: Critical evaluation of laboratory procedures in the study of the patient. Edited by Thomas H. Ham, M.D., assistant professor of medicine, Harvard Medical School, associate director, Thorndike Memorial Laboratory, and junior visiting physician, Boston City Hospital. 4°, paper, 496 pp., with illustrations. Cambridge, Massachusetts: Harvard University Press, 1950. $5.00.

This composite syllabus is the joint work of 33 contributors, many of them from Boston institutions. Sixty-six specialists criticized the various methods. The text is divided into seven principal parts: introduction to laboratory examinations, laboratory examinations of blood, urinary system and diseases of the gastrointestinal tract and special tests related to infectious diseases, diseases of metabolism and extravascular fluids. There are a total of 27 chapters, to which lists of references are appended. There is a good index, and the price is low. The book should be in all collections on clinical medicine.

An Atlas of Human Anatomy. By Barry J. Anson, Ph.D., professor of anatomy, Northwestern University Medical School. 4°, cloth, 518 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1950. $11.50.

This new topographic atlas of anatomy compares favorably with the well known German atlases of Spalteholz and Sobotta. The material is divided into sections on the head, neck, upper extremity, back and thorax, abdomen, pelvis and perineum, and lower extremity. There is a good index, and the plate work, both color and black and white, is superb. The atlas should be in all collections on anatomy. The price is low for the type of book.

Pathologic Physiology: Mechanisms of disease. Edited by William A. Sodeman, M.D., William Henderson Professor of the Prevention of Tropical and Semi-Tropical Diseases, Tulane University of Louisiana School of Medicine, senior visiting physician, Charity Hospital of Louisiana, and consultant in medicine, United States Marine Hospital at New Orleans. 8°, cloth, 808 pp., with 146 illustrations and 30 tables. Philadelphia: W. B. Saunders Company, 1950. $11.50.

This composite work is the joint effort of 25 contributors. The approach to problems in the field of internal medicine is made from the standpoint of disturbed physiology. The text is divided into nine parts on the circulatory, respiratory and digestive systems, blood and spleen, urinary tract, endocrine glands, water balance and nutrition, locomotor system, infectious diseases and allergy, and physical, toxic and chemical agents. Lists of references are appended to the various parts. The book is well published. It is recommended for all medical libraries and the libraries of internists.

The Closed Treatment of Common Fractures. By John Charnley, M.B., F.R.C.S., assistant honorary orthopaedic surgeon, Manchester Royal Infirmary, visiting orthopaedic surgeon, Park Hospital, Davyhulme, and lecturer in orthopaedics, Manchester University. 8°, cloth, 190 pp., with 133 illustrations. Baltimore: Williams and Wilkins Company, 1950. $7.00.

This monograph has been written primarily for resident casualty surgeons in hospitals. It naturally reflects British practice. The preliminary chapters are devoted to a consideration of conservative treatment and plaster technic. The remaining chapters discuss the treatment of the various types of fractures of the extremities. The text is condensed and the material well arranged and well illustrated. There is an index, and the book is well published. The printing was done in Great Britain.

Therapeutics in Internal Medicine. Edited by Franklin A. Kyser, M.D., M.S., associate in medicine, Northwestern University Medical School, and attending physician, Evanston Hospital, Evanston, Illinois. 8°, cloth, 715 pp. New York: Thomas Nelson and Sons, 1950. $12.00.

This new book on treatment is the joint work of 81 contributors. The whole field of medicine is covered in 17 chapters. All articles are signed by the authors. The material is condensed for practical purposes, and the book should prove valuable as a ready reference source to the practicing physician. Lists of selected references are appended to the various subjects. A two-column type setup is used to conserve space. There is a comprehensive index, and the book is well published.

The Biology of Human Starvation. By Ancel Keys, Josef Brozek, Austin Henschel, Olaf Mickelsen and Henry L. Taylor. With the assistance of Ernst Simonson, Angie S. Skinner and Samuel M. Wells, of the Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota. With forewords by J. C. Drummond, Russell M. Wilder, Charles G. King and Robert R. Williams. In 2 volumes. 8°, cloth. Vol. I, 763 pp., with 359 tables. Vol. II, 618 pp., with 205 tables. Minneapolis: University of Minnesota Press, 1950. $24.00 for the set.

This comprehensive study of all the aspects of human starvation and undernutrition should be in all collections on physiology and on nutrition and its disorders. The first volume comprises the material on morphology, biochemistry and physiology, with a historical introduction. The second vol-

ume discusses the psychologic aspects and special problems, including edema, anorexia nervosa and pituitary cachexia, growth and development, tuberculosis, undernutrition and infectious diseases and diabetes mellitus, cancer and other neoplasms, and diets for rehabilitation, with special reference to the Minnesota experiment. This experiment was carried out on 32 volunteers from November 19, 1944, to October 20, 1945. The subjects were in continuous residence at the Laboratory of Physiological Hygiene during this period. They were given a twelve-week control period, twenty-four weeks of semistarvation, and twelve weeks of restricted rehabilitation. The results of this experiment constitute the material on which this work is based. A comprehensive bibliography of 86 pages is appended to the text. There is a good index, and the work is well published.

Anxiety. Edited by Paul H. Hoch, M.D., New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons, and Joseph Zubin, Ph.D., New York State Psychiatric Institute, Department of Psychology, Columbia University. New York: Grune and Stratton, 1950. $4.50. (The proceedings of the thirty-ninth annual meeting of the American Psychopathological Association, held in New York City in June, 1949.)

These proceedings contain papers by fourteen contributors on various aspects of anxiety. The material is divided into five parts on the historical and social approach, the psychologic approach, the clinical and psychoanalytic approach, the physiologic approach and the president's address by Dr. Hoch on the biosocial aspects of anxiety. There is an index, and the book is well published. It should be in all collections on psychiatry and abnormal psychology.

Handbook of Antibiotics. By A. L. Baron, Research Division, S. B. Penick Co. 8°, cloth, 303 pp. New York: Reinhold Publishing Corporation, 1950. $6.50.

This handbook is an essential reference work and should be in all medical libraries. The various antibiotics are arranged in alphabetical order, with a list of selected references for each substance. There are indexes of authors and organisms. A glossary of special terms is appended to the text.

Einführung in die Hals-Nasen-Ohrenheilkunde. By Paul Falk, ordentlicher Professor der Oto-Rhino-Laryngologie und Direktor der Hals-Nasen-Ohren Klinik der Universität des Saarlandes in Homburg (Saar). Second edition. 8°, cloth, 175 pp., with 150 illustrations. Stuttgart, Germany: Georg Thieme, 1950. Ganzleinen DM 19.80. Distributed by Grune and Stratton, Inc., New York City.

This second edition of a manual on the ear, nose and throat has been revised to bring it up to date. The text is divided into six parts on the ear, nose and sinuses, mouth, pharynx, larynx and trachea, bronchi and esophagus. An appendix comprises a comparative list of the old and new anatomical names of the B.N.A. of 1895 and the I.N.A. of 1935. There is a good index of subjects, the illustrations, in color or black and white, are excellent and the book is well published.

Problems in Cerebellar Physiology. By G. Moruzzi, M.D., professor and head of the Department of Physiology, University of Pisa, Italy, and annual research professor of neurology, Northwestern University Medical School, Chicago, Illinois. 12°, cloth, 116 pp., with 15 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $3.25.

In this monograph the author deals with cerebral inhibition and facilitation of postural tonus, functional interrelations between cerebellum and cerebral motor cortex and the cerebellar influence in the autonomic sphere. A bibliography of 86 titles concludes the text.

Color Atlas of Pathology. Prepared under the auspices of the United States Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 8°, cloth, 546 pp., with 1053 illustrations. Philadelphia, Pennsylvania: J. B. Lippincott Company, 1950. $20.00.

The material used in this new atlas of pathology was selected from the collections of the Pathology Department of the Naval Medical School, the Army Institute of Pathology, Johns Hopkins Hospital and Georgetown University School of Medicine. The color pictures and descriptive text are printed on the same page, a procedure making for easy reference — aside from the plates on the blood, which are full-page plates. There is a comprehensive index. The publishing is excellent, and the atlas should be in all collections on pathology.

The Image and Appearance of the Human Body. Studies in the constructive energies of the psyche. By Paul Schilder, M.D., Ph.D., research professor of psychiatry, New York University, clinical director, Bellevue Psychiatric Hospital, New York, and associate professor of psychiatry, University of Vienna. 8°, cloth, 352 pp., with 7 illustrations. New York: International Universities Press, Inc., 1950. $4.50.

In this monograph are discussed the physiologic basis, the libidinous structure and the sociology of the body-image. This image is defined as the "picture of our body which we form in our mind." There is a bibliography, and indexes of authors and subjects.

The Preparation of Photographic Prints for Medical Publication. By Stanley J. McComb, F.B.P.A., Section on Photography, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 69 pp., with 21 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00. Publication Number 90, American Lecture Series.

This practical manual discusses the essentials of good medical illustration, the proper preparation for photography and the finishing of the photograph for publication. The various figures in the text are fine examples of medical illustration.

Indications for and Results of Splenectomy. By Frederick A. Coller, M.D., Alexander Blain, III, M.D., and Gould Andrews, M.D., from the departments of Surgery and Medicine, University of Michigan Medical School. 8°, paper, 100 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.25. Publication Number 86, American Lecture Series.

In this small monograph splenectomy has been discussed on the basis of 132 consecutive operations. The over-all hospital mortality was 7.6 per cent, an improvement over the mortality for 1920–1935. The eventual mortality associated with diseases for which splenectomy was performed was 16 per cent. The authors are convinced that splenectomy offers a specific cure for essential thrombocytopenic purpura and congenital and some cases of acquired hemolytic anemia and for selected cases of Banti's syndrome, and that it appears to be a worth-while procedure in other diseases of the spleen.

Food Allergy. By Herbert J. Rinkel, M.D., Theron G. Randolph, M.D., instructor in medicine, Northwestern University Medical School, and Michael Zeller, M.D., clinical instructor in medicine, University of Illinois College of Medicine. 8°, cloth, 492 pp., with 22 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $8.50.

This new book on food allergy is based mainly on clinical observations made during thousands of individual food tests. The text is well written and organized and covers the various aspects of the subject. Emphasis is placed on symptomatology, diagnosis and treatment. An appendix of 98 pages is devoted to the Food, Drug and Cosmetic Act. The book is well published and should be in all collections on the subject.

Pharmacological Basis of Penicillin Therapy. By Karl H. Beyer, Ph.D., M.D., director of pharmacological research, Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pennsylvania. 8°, cloth, 214 pp., with 35 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $4.50. Publication Number 77, American Lecture Series.

This scientific monograph discusses the pharmacology and physiology of penicillin and carinamide and their clinical uses. There is an appendix on the new agent benemid. Lists of references are appended to the six chapters of the text and there is a good index. The monograph should be in all medical libraries and available to all physicians interested in penicillin therapy.

When Minds Go Wrong: A simple story of the mentally ill — past, present, and future. 8°, cloth, 237 pp., with illustrations. Chicago, Illinois: John M. Grimes, 1949. $5.00.

In this book Dr. Grimes tells the story of the care of the mentally ill.

Klinische Physiologie und Pathologie. By Prof. Dr. Ferdinand Hoff, Vorstand der medizinischen Klinik der stadtischen Krankenanstalten Aachen. 8°, cloth, 782 pp., 124 illustrations. Stuttgart, Germany: Georg Thieme, 1950. Ganzleinen DM 39. Distributed by Grune and Stratton, Inc., New York.

This textbook of physiologic pathology is comprehensive in its scope. The text is arranged in order of the systems and organs of the body. The last chapters deal with the vegetative nervous system, internal secretions and metabolism. There is a bibliography of selected references, and indexes of authors and subjects. The publishing is excellent, and the book should be in all collections on the subject.

Hygiene und Korperschulung der Frau. By Prof. Dr. F. A. Wahl, Oberarzt der Universitäts-Frauenklinik, Köln. 8°, cloth, 166 pp., with 62 illustrations. Stuttgart, Germany: Georg Thieme, 1950. Ganzleinen DM 16.80. Distributed by Grune and Stratton, Inc., New York.

This book on hygiene and body culture for women is comprehensive in its scope. The material is well arranged and the text is well written. The illustrations are good and the publishing is excellent. A bibliography of thirteen pages concludes the text. Surprisingly, the book lacks an index, but there is a detailed table of contents.

A Symposium on Steroid Hormones. Edited by Edgar S. Gordon. 8°, cloth, 396 pp., with illustrations. Madison, Wisconsin: The University of Wisconsin Press, 1950. $6.50.

This composite volume is the joint work of 34 contributors. The various aspects of the steroid hormones are discussed, including metabolism, effects on cancer and sex determination and differentiation. Lists of references are appended to the chapters, and the book is well published. An index would make the book more valuable for reference purposes. The work should be in all collections on the hormones.

An Outline of Scientific Criminology. By Nigel Morland. 12°, cloth, 287 pp., with 12 illustrations. New York: Philosophical Library, Inc., 1950. $6.25.

In this small book the author has condensed the present-day knowledge of scientific identification of individuals, documents, secret writing and stains. There is a chapter on forensic chemistry, and one on the applications of scientific criminology. There is an index, and the book is well published. The printing was done in Great Britain. The book should be in all medicolegal collections.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

The next meeting of the New England Pediatric Society will be held on Wednesday, September 19. The Medical Clinic will be held at 11:00 a.m. in the main amphitheatre, Peter Bent Brigham Hospital, Boston. The Clinicopathological Conference will be held at 12:00 m., in the main amphitheatre, Peter Bent Brigham Hospital. The afternoon session will be held at 2:15 p.m. in Amphitheatre C, Harvard Medical School.

The evening meeting will be held at Longwood Towers, Brookline. Dr. Charles F. McKhann will talk on "The Problem of Mental Retardation and Cerebral Palsy."

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The Massachusetts Academy of General Practice will present a Clinical Assembly on September 26. The morning clinic will be held at Beth Israel Hospital; afternoon and evening clinical meetings will take place at the Hotel Shelton, Boston.

POSTGRADUATE SEMINAR IN NEUROLOGY AND PSYCHIATRY

The Massachusetts Department of Mental Health announces the Seventeenth Postgraduate Seminar in Neurology and Psychiatry, to be given under the auspices of the Metropolitan State Hospital and the Psychiatric Training Faculty of Massachusetts, Incorporated. The course will comprise 70 lectures, to be given every Monday, 2:00 p.m. to 8:30 p.m., from October 1 to December 3, 1951, and from March 3 to May 5, 1952, at the Metropolitan State Hospital, 475 Trapelo Road, Waltham, Massachusetts.

All interested graduate physicians should apply in writing, before October 1, 1951, to: Dr. William C. Gaebler, Superintendent, Metropolitan State Hospital, Waltham, Massachusetts.

MARKLE SCHOLAR IN MEDICAL SCIENCE NOMINATIONS

The John and Mary R. Markle Foundation invites deans of medical schools in the United States and Canada to make nominations for the fifth group of Scholars in Medical Science on or before December 1, 1951. Each school may nominate one candidate.

Candidates should have completed the usual fellowship training in some area of science related to medicine and should hold, or expect to hold, in the academic year 1952-1953, a full-time faculty appointment on the staff of a medical school. The grants are not intended for the support of interns or residents or for those regarded by the faculty as advanced students still in training.

Grants of $30,000, payable at the rate of $6000 annually, will be made to the schools over a five-year period toward the support of each scholar and his research. The number of scholars to be appointed in 1952 has not yet been determined. Twenty were named in 1950 and in 1951. A new booklet about the plan, with suggestions for making nominations, is available on request from the Foundation, 14 Wall Street, New York 5, New York.

GRANTS AND FELLOWSHIPS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for grants and fellowships. Applications for new grants will be received until October 1. Investigators now receiving grants will be notified individually concerning application for extension of these grants. Final decision on grant applications will be made early in 1952. Grants approved at this time will ordinarily become effective July 1, 1952.

Applications for American Cancer Society Fellowships in Cancer Research received prior to November 1 will be acted on by the Committee on Growth in December. Those received between November 1 and March 1 will be acted on in April. Fellowships will ordinarily begin July 1, although this date may be varied at the request of the applicant. Details about the availability of Damon Runyon Fellowships will be announced later.

During the past year the American Cancer Society, Incorporated, on recommendation of the Committee on Growth, has awarded grants and fellowships approximating $2,000,000. A program of similar magnitude is contemplated for the coming year.

Application blanks and additional information may be obtained from the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

AMERICAN COLLEGE OF SURGEONS

The American College of Surgeons will hold its thirty-seventh annual Clinical Congress in San Francisco, November 5-9, 1951, with headquarters at the Fairmont Hotel and the Civic Auditorium. The thirtieth annual Hospital Standardization Conference is scheduled to be held concurrently, with meetings in the Civic Auditorium, as a part of the Congress. The combined programs will include scientific and technical exhibits, color television, cine clinics, medical motion pictures, scientific sessions, panel discussions, conferences, symposia, official meetings and forums.

(*Notices concluded on page xvii*)